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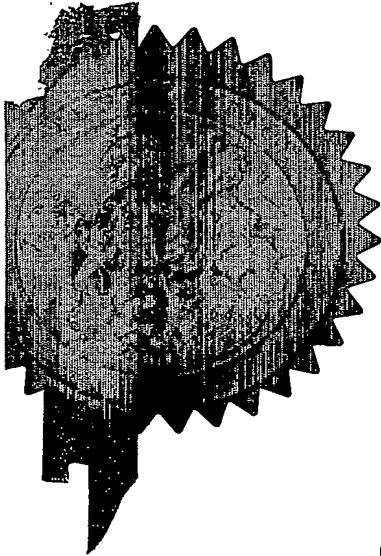
PCT

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# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference

RJW/CP6071971 11NOV02 E762241-1 D00060  
P01/7700 0:00-0226149.3

2. Patent application number  
(The Patent Office will fill in this part)

0226149.3

3. Full name, address and postcode of the or of each applicant (underline all surnames)

ASTEX TECHNOLOGY LTD  
250 Cambridge Science Park  
Milton Road  
CAMBRIDGE  
CB4 0WE

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

ENGLAND

8118317001

4. Title of the invention

INHIBITORS

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

MEWBURN ELLIS  
York House  
23 Kingsway  
London WC2B 6HP

Patents ADP number (if you know it)

109006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

YES

- a) any applicant named in part 3 is not an inventor, or
  - b) there is an inventor who is not named as an applicant, or
  - c) any named applicant is a corporate body.
- See note (d))

# Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	103 <i>RM</i>
Claim(s)	0
Abstract	0
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

*Robert J Watson*

Date

8 November 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

ROBERT J WATSON  
020 7240 4405

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## Notes

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## Inhibitors

This invention relates to pyridine and pyrazine derivatives which inhibit the activity of p38 MAP kinase, and the use of these compounds as pharmaceuticals.

### Background

Mitogen-activated protein (MAP) kinases are proline-directed kinases that mediate the effects of numerous extracellular stimuli on a wide array of biological processes, such as cell proliferation, differentiation and death. Three groups of mammalian MAP kinases have been studied in detail: the extracellular signal-regulated kinases (ERK), the c-Jun NH<sub>2</sub>-terminal kinases (JNK) and the p38 MAP kinases.

There are five known human isoforms of p38 MAP kinase, p38 $\alpha$ , p38 $\beta$ , p38 $\beta$ 2, p38 $\gamma$  and p38 $\delta$ . The p38 kinases, which are also known as cytokine suppressive anti-inflammatory drug binding proteins (CSBP), stress activated protein kinases (SAPK) and RK, are responsible for phosphorylating and activating transcription factors as well as other kinases, and are themselves activated by physical and chemical stress (e.g. UV, osmotic stress), pro-inflammatory cytokines and bacterial lipopolysaccharide (LPS) (Herlaar, E & Brown, Z., *Molecular Medicine Today*, 5: 439-447 (1999)). The products of p38 phosphorylation have been shown to mediate the production of inflammatory cytokines, including TNF and IL-1, and cyclooxygenase-2 (COX-2). Each of these cytokines has been implicated in numerous disease states and conditions. IL-1 and TNF are also known to stimulate the production of other proinflammatory cytokines such as IL-6 and IL-8.

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation (e.g. Dinarello, et al., *Rev. Infect. Disease*, 6: 51

(1984)). The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Evidence also links IL-1 activity to diabetes and pancreatic B cells (Dinarello, *J. Clinical Immunology*, 5: 287-297 (1985)).

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury , graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

Interleukin-8 (IL-8) is a chemotactic factor produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1 , TNF , or lipopolysachharide (LPS). IL-8

stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T -lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as

5 Iysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD 11 b/CD 18) on neutrophils without de novo protein synthesis; this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are

10 characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophil into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production. Recently Chronic Obstructive Pulmonary Disease

15 (COPD) has been linked to raised levels of IL-8 (Barnes et al., *Curr. Opin. Pharmacol.*, 1: 242-7 (2001)). Other conditions linked to IL-8 include acute respiratory distress syndrome (ARDS), asthma, pulmonary fibrosis and bacterial pneumonia.

20 IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating

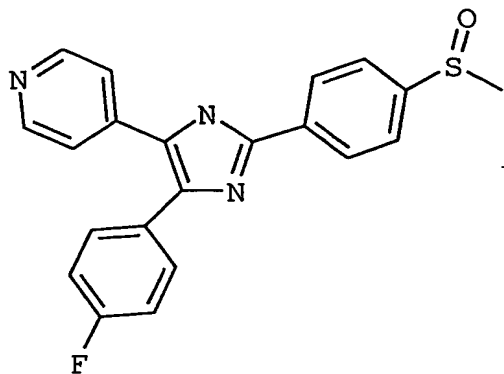
25 many of these disease states.

Inhibition of signal transduction via p38, which in addition to IL-1, TNF and IL-8 described above is also required for the synthesis and/or action of several additional pro-inflammatory

30 proteins (i.e., IL-6, GM-CSF, COX-2, collagenase and stromelysin), is expected to be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. This expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors

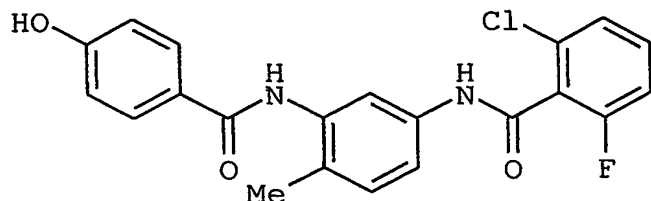
35 (Badger, et al., *J. Pharm. Exp. Thera.*, 279: 1453-1461 (1996); Griswold, et al., *Pharmacol. Comm.*, 7: 323-229 (1996)).

A number of inhibitors of p38 MAP kinase have been previously disclosed. Smith-Kline Beecham's SB 203580 (see WO 93/14081) has the structure:



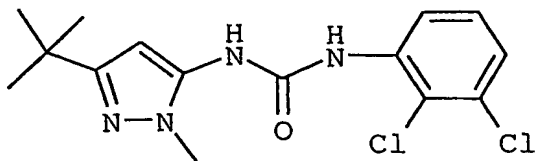
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Zeneca have derived (WO 99/15164) compounds having structures related to:



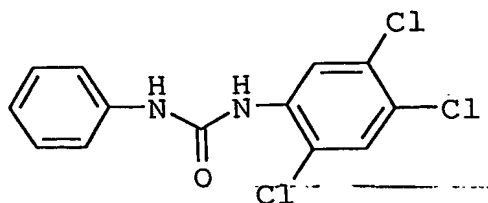
10 which exhibit inhibition of p38 activity.

Bayer have disclosed a series of compounds which act as p38 MAP kinase inhibitors (WO 99/32111); one such compound has the structure:



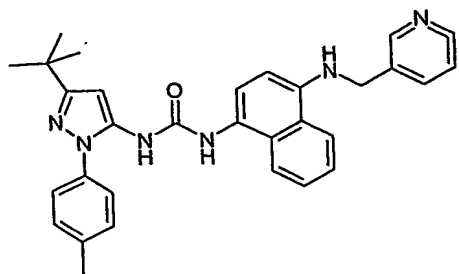
15

Vertex have developed compounds as p38 MAP kinase inhibitors, with structures such as that shown below (WO 99/00357).



Boehringer Ingelheim have disclosed numerous compounds said to inhibit proinflammatory cytokines, such as TNF and IL-1, in, for example WO 00/43384. An example of a compound disclosed in that

5 patent application is:

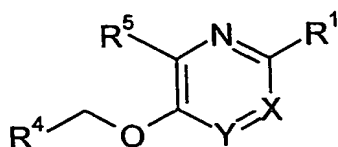


# Summary of the Invention

The present inventors have discovered that certain pyridine and

10 pyrazine derivatives can be used as pharmaceuticals, and in particular can be used to inhibit the activity of p38 MAP kinase.

Accordingly, the first aspect of the present invention provides a compound of the formula I:



15 wherein:

-X=Y- is selected from -CR<sup>2</sup>=CR<sup>3</sup>- and -CR<sup>2</sup>=N-;

R<sup>1</sup> is selected from H, halo, NRR', NHC(=O)R, NHC(=O)NRR', NH<sub>2</sub>SO<sub>2</sub>R, and C(=O)NRR', where R and R' are independently selected from H and C<sub>1-4</sub> alkyl, and are optionally substituted by OH, NH<sub>2</sub>, SO<sub>2</sub>-NH<sub>2</sub>,

20 C<sub>5-20</sub> carboaryl, C<sub>5-20</sub> heteroaryl and C<sub>3-20</sub> heterocyclyl, or may together form, with the nitrogen atom to which they are attached, an optionally substituted nitrogen containing C<sub>5-7</sub> heterocyclyl group;

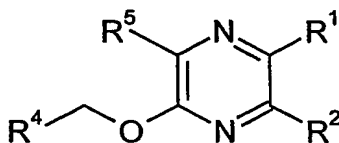
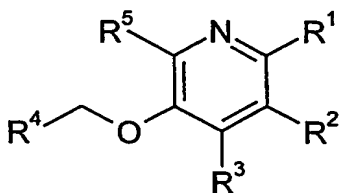


$R^2$  and  $R^3$  (where present) are independently selected from H, optionally substituted  $C_{1-7}$  alkyl, optionally substituted  $C_{5-20}$  aryl, optionally substituted  $C_{3-20}$  heterocyclyl, halo, amino, amido, hydroxy, ether, thio, thioether, acylamido, ureido and sulfonamino;

$R^4$  an optionally substituted  $C_{5-20}$  aryl or  $C_{5-20}$  heteroaryl group; and

$R^5$  is selected from  $R^{5'}$ , halo,  $NHR^{5'}$ ,  $C(=O)NHR^{5'}$ ,  $OR^{5'}$ ,  $SR^{5'}$ ,  $NHC(=O)R^{5'}$ ,  $NHC(=O)NHR^{5'}$ ,  $NHS(=O)_2R^{5'}$ , wherein  $R^{5'}$  is H or  $C_{1-3}$  alkyl (optionally substituted by halo,  $NH_2$ , OH, SH); and pharmaceutically acceptable salts thereof for use in a method of therapy.

The two possibilities for  $-X=Y-$  result in compounds of formulae Ia and Ib:



where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined above.

A second aspect of the present invention provides a composition comprising a compound of the first aspect and a pharmaceutically acceptable carrier or diluent.

A third aspect of the present invention provides the use of a compound of the first aspect of the invention for the manufacture of a medicament for use in the treatment of condition ameliorated by the inhibition of p38 MAP kinase.

Conditions ameliorated by the inhibition of p38 MAP kinase are discussed above, and include, but are not limited to, rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, and other arthritic conditions; Alzheimer's disease; toxic shock syndrome, the inflammatory reaction induced by

endotoxin or inflammatory bowel disease; tuberculosis,  
atherosclerosis, muscle degeneration, Reiter's syndrome, gout,  
acute synovitis, sepsis, septic shock, endotoxic shock, gram  
negative sepsis, adult respiratory distress syndrome, cerebral  
5 malaria, chronic pulmonary inflammatory disease, silicosis,  
pulmonary sarcoisosis, bone resorption diseases, reperfusion  
injury , graft vs. host reaction, allograft rejections, fever and  
myalgias due to infection, such as influenza, cachexia, in  
particular cachexia secondary to infection or malignancy,  
10 cachexia secondary to acquired immune deficiency syndrome (AIDS),  
AIDS, ARC (AIDS related complex), keloid formation, scar tissue  
formation, Crohn's disease, ulcerative colitis, pyresis, chronic  
obstructive pulmonary disease (COPD), acute respiratory distress  
syndrome (ARDS), asthma, pulmonary fibrosis and bacterial  
15 pneumonia.

Thus, further aspects of the present invention provide the use of  
a compound of the first aspect of the invention for the  
manufacture of a medicament for use in the treatment of arthritic  
20 conditions.

Another aspect of the invention provides a compound of the first  
aspect of the invention for use in a method of treatment of the  
human or animal body.

25 Another aspect of the invention provides a method of inhibiting  
p38 MAP kinase, *in vitro* or *in vivo*, comprising contacting a cell  
with an effective amount of a compound of the first aspect of the  
invention.

30 Another aspect of the invention pertains to a method for the  
treatment of a condition ameliorated by the inhibition of p38 MAP  
kinase comprising administering to a subject suffering from said  
a condition ameliorated by the inhibition of p38 MAP kinase a  
35 therapeutically-effective amount of a compound of the first  
aspect of the invention.

### Definitions

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

5

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

10

15 The substituents, and groups listed above, are described in more detail below.

C<sub>1-7</sub> alkyl: The term "C<sub>1-7</sub> alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 7 carbon atoms, which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, etc., discussed below.

20

25

Examples of saturated alkyl groups include, but are not limited to, methyl (C<sub>1</sub>), ethyl (C<sub>2</sub>), propyl (C<sub>3</sub>), butyl (C<sub>4</sub>), pentyl (C<sub>5</sub>), hexyl (C<sub>6</sub>) and heptyl (C<sub>7</sub>).

30

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C<sub>1</sub>), ethyl (C<sub>2</sub>), n-propyl (C<sub>3</sub>), n-butyl (C<sub>4</sub>), n-pentyl (amyl) (C<sub>5</sub>), n-hexyl (C<sub>6</sub>), and n-heptyl (C<sub>7</sub>).

35

Examples of saturated branched alkyl groups include iso-propyl (C<sub>3</sub>), iso-butyl (C<sub>4</sub>), sec-butyl (C<sub>4</sub>), tert-butyl (C<sub>4</sub>), iso-pentyl (C<sub>5</sub>), and neo-pentyl (C<sub>5</sub>).

C<sub>3-7</sub> Cycloalkyl: The term "C<sub>3-7</sub> cycloalkyl" as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 7 ring atoms. Preferably, each ring has from 3 to 7 ring atoms.

Examples of saturated cylcoalkyl groups include, but are not limited to, those derived from: cyclopropane (C<sub>3</sub>), cyclobutane (C<sub>4</sub>), cyclopentane (C<sub>5</sub>), cyclohexane (C<sub>6</sub>) and cycloheptane (C<sub>7</sub>).

C<sub>2-7</sub> Alkenyl: The term "C<sub>2-7</sub> alkenyl" as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds.

Examples of unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH<sub>2</sub>), 1-propenyl (-CH=CH-CH<sub>3</sub>), 2-propenyl (allyl, -CH=CH-CH<sub>2</sub>), isopropenyl (-C(CH<sub>3</sub>)=CH<sub>2</sub>), butenyl (C<sub>4</sub>), pentenyl (C<sub>5</sub>), and hexenyl (C<sub>6</sub>).

Examples of unsaturated cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not limited to, cyclopropenyl (C<sub>3</sub>), cyclobutenyl (C<sub>4</sub>), cyclopentenyl (C<sub>5</sub>), and cyclohexenyl (C<sub>6</sub>).

C<sub>2-7</sub> Alkynyl: The term "C<sub>2-7</sub> alkynyl", as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds.

Examples of unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, -C≡CH) and 2-propynyl (propargyl, -CH<sub>2</sub>-C≡CH).

C<sub>1-4</sub> alkyl: The term "C<sub>1-4</sub> alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 4 carbon atoms, which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "C<sub>1-4</sub> alkyl" includes the sub-classes "C<sub>2-4</sub> alkenyl", "C<sub>2-4</sub>

alkynyl" and "C<sub>2-4</sub> cycloalkyl". Examples of these moieties are given above.

5 C<sub>3-20</sub> Heterocyclyl: The term "C<sub>3-20</sub> heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms, of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms, which include N, O and  
10 S.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

15 N<sub>1</sub>: aziridine (C<sub>3</sub>), azetidine (C<sub>4</sub>), pyrrolidine (tetrahydropyrrole) (C<sub>5</sub>), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C<sub>5</sub>), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C<sub>5</sub>), piperidine (C<sub>6</sub>), dihydropyridine (C<sub>6</sub>), tetrahydropyridine (C<sub>6</sub>), azepine (C<sub>7</sub>);

20 O<sub>1</sub>: oxirane (C<sub>3</sub>), oxetane (C<sub>4</sub>), oxolane (tetrahydrofuran) (C<sub>5</sub>), oxole (dihydrofuran) (C<sub>5</sub>), oxane (tetrahydropyran) (C<sub>6</sub>), dihydropyran (C<sub>6</sub>), pyran (C<sub>6</sub>), oxepin (C<sub>7</sub>);

25 S<sub>1</sub>: thiirane (C<sub>3</sub>), thietane (C<sub>4</sub>), thiolane (tetrahydrothiophene) (C<sub>5</sub>), thiane (tetrahydrothiopyran) (C<sub>6</sub>), thiepane (C<sub>7</sub>);

O<sub>2</sub>: dioxolane (C<sub>5</sub>), dioxane (C<sub>6</sub>), and dioxepane (C<sub>7</sub>);

30 O<sub>3</sub>: trioxane (C<sub>6</sub>);

N<sub>2</sub>: imidazolidine (C<sub>5</sub>), pyrazolidine (diazolidine) (C<sub>5</sub>), imidazoline (C<sub>5</sub>), pyrazoline (dihydropyrazole) (C<sub>5</sub>), piperazine (C<sub>6</sub>);

35

N<sub>1</sub>O<sub>1</sub>: tetrahydrooxazole (C<sub>5</sub>), dihydrooxazole (C<sub>5</sub>),  
tetrahydroisoxazole (C<sub>5</sub>), dihydroisoxazole (C<sub>5</sub>), morpholine (C<sub>6</sub>),  
tetrahydrooxazine (C<sub>6</sub>), dihydrooxazine (C<sub>6</sub>), oxazine (C<sub>6</sub>);

5 N<sub>1</sub>S<sub>1</sub>: thiazoline (C<sub>5</sub>), thiazolidine (C<sub>5</sub>), thiomorpholine (C<sub>6</sub>);

N<sub>2</sub>O<sub>1</sub>: oxadiazine (C<sub>6</sub>);

O<sub>1</sub>S<sub>1</sub>: oxathiole (C<sub>5</sub>) and oxathiane (thioxane) (C<sub>6</sub>); and,

10

N<sub>1</sub>O<sub>1</sub>S<sub>1</sub>: oxathiazine (C<sub>6</sub>).

Nitrogen containing C<sub>5-7</sub> heterocyclyl: The term "nitrogen  
containing C<sub>5-7</sub> heterocyclyl" as used herein, pertains to a  
15 monovalent moiety obtained by removing a hydrogen atom from a  
ring atom of a heterocyclic compound, which moiety has from 5 to  
7 ring atoms, of which a least one is a nitrogen ring atom.  
Examples of nitrogen containing C<sub>5-7</sub> heterocyclyl groups include,  
but are not limited to, those derived from:

20

N<sub>1</sub>: pyrrolidine (tetrahydropyrrole) (C<sub>5</sub>), pyrroline (e.g.,  
3-pyrroline, 2,5-dihydropyrrole) (C<sub>5</sub>), 2H-pyrrole or 3H-pyrrole  
(isopyrrole, isoazole) (C<sub>5</sub>), piperidine (C<sub>6</sub>), dihydropyridine  
(C<sub>6</sub>), tetrahydropyridine (C<sub>6</sub>), azepine (C<sub>7</sub>);

25

N<sub>2</sub>: imidazolidine (C<sub>5</sub>), pyrazolidine (diazolidine) (C<sub>5</sub>),  
imidazoline (C<sub>5</sub>), pyrazoline (dihydropyrazole) (C<sub>5</sub>), piperazine  
(C<sub>6</sub>);

30

N<sub>1</sub>O<sub>1</sub>: tetrahydrooxazole (C<sub>5</sub>), dihydrooxazole (C<sub>5</sub>),  
tetrahydroisoxazole (C<sub>5</sub>), dihydroisoxazole (C<sub>5</sub>), morpholine (C<sub>6</sub>),  
tetrahydrooxazine (C<sub>6</sub>), dihydrooxazine (C<sub>6</sub>), oxazine (C<sub>6</sub>);

N<sub>1</sub>S<sub>1</sub>: thiazoline (C<sub>5</sub>), thiazolidine (C<sub>5</sub>), thiomorpholine (C<sub>6</sub>);

35

N<sub>2</sub>O<sub>1</sub>: oxadiazine (C<sub>6</sub>);

N<sub>2</sub>S<sub>1</sub>: thiadiazole (C<sub>5</sub>); and,

N<sub>1</sub>O<sub>1</sub>S<sub>1</sub>: oxathiazine (C<sub>6</sub>).

5 C<sub>5-20</sub> carboaryl: The term "C<sub>5-20</sub> carboaryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 20 carbon ring atoms. Preferably, each ring has from 5 to 7 ring atoms.

10

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e. phenyl) (C<sub>6</sub>), naphthalene (C<sub>10</sub>), azulene (C<sub>10</sub>), anthracene (C<sub>14</sub>), phenanthrene (C<sub>14</sub>), naphthacene (C<sub>18</sub>), and pyrene (C<sub>16</sub>).

15

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C<sub>9</sub>), isoindene (C<sub>9</sub>), and fluorene (C<sub>13</sub>).

20

C<sub>5-20</sub> heteroaryl: The term "C<sub>5-20</sub> heteroaryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 20 ring atoms, which include one or more  
25 heteroatoms. Preferably, each ring has from 5 to 7 ring atoms.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N<sub>1</sub>: pyrrole (azole) (C<sub>5</sub>), pyridine (azine) (C<sub>6</sub>);

30 O<sub>1</sub>: furan (oxole) (C<sub>5</sub>);

S<sub>1</sub>: thiophene (thiole) (C<sub>5</sub>);

N<sub>1</sub>O<sub>1</sub>: oxazole (C<sub>5</sub>), isoxazole (C<sub>5</sub>), isoxazine (C<sub>6</sub>);

N<sub>2</sub>O<sub>1</sub>: oxadiazole (furazan) (C<sub>5</sub>);

N<sub>3</sub>O<sub>1</sub>: oxatriazole (C<sub>5</sub>);

35 N<sub>1</sub>S<sub>1</sub>: thiazole (C<sub>5</sub>), isothiazole (C<sub>5</sub>);

N<sub>2</sub>: imidazole (1,3-diazole) (C<sub>5</sub>), pyrazole (1,2-diazole) (C<sub>5</sub>),  
pyridazine (1,2-diazine) (C<sub>6</sub>), pyrimidine (1,3-diazine) (C<sub>6</sub>)  
(e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C<sub>6</sub>);  
N<sub>3</sub>: triazole (C<sub>5</sub>), triazine (C<sub>6</sub>); and,  
5 N<sub>4</sub>: tetrazole (C<sub>5</sub>).

Examples of heteroaryl groups which comprise fused rings,  
include, but are not limited to:

C<sub>9</sub> heteroaryl groups (with 2 fused rings) derived from  
10 benzofuran (O<sub>1</sub>), isobenzofuran (O<sub>1</sub>), indole (N<sub>1</sub>), isoindole (N<sub>1</sub>),  
indolizine (N<sub>1</sub>), indoline (N<sub>1</sub>), isoindoline (N<sub>1</sub>), purine (N<sub>4</sub>)  
(e.g., adenine, guanine), benzimidazole (N<sub>2</sub>), indazole (N<sub>2</sub>),  
benzoxazole (N<sub>1</sub>O<sub>1</sub>), benzisoxazole (N<sub>1</sub>O<sub>1</sub>), benzodioxole (O<sub>2</sub>),  
benzofurazan (N<sub>2</sub>O<sub>1</sub>), benzotriazole (N<sub>3</sub>), benzothiofuran (S<sub>1</sub>),  
15 benzothiazole (N<sub>1</sub>S<sub>1</sub>), benzothiadiazoole (N<sub>2</sub>S);

C<sub>10</sub> heteroaryl groups (with 2 fused rings) derived from  
chromene (O<sub>1</sub>), isochromene (O<sub>1</sub>), chroman (O<sub>1</sub>), isochroman (O<sub>1</sub>),  
benzodioxan (O<sub>2</sub>), quinoline (N<sub>1</sub>), isoquinoline (N<sub>1</sub>), quinolizine  
(N<sub>1</sub>), benzoxazine (N<sub>1</sub>O<sub>1</sub>), benzodiazine (N<sub>2</sub>), pyridopyridine (N<sub>2</sub>),  
20 quinoxaline (N<sub>2</sub>), quinazoline (N<sub>2</sub>), cinnoline (N<sub>2</sub>), phthalazine  
(N<sub>2</sub>), naphthyridine (N<sub>2</sub>), pteridine (N<sub>4</sub>);

C<sub>13</sub> heteroaryl groups (with 3 fused rings) derived from  
carbazole (N<sub>1</sub>), dibenzofuran (O<sub>1</sub>), dibenzothiophene (S<sub>1</sub>),  
carboline (N<sub>2</sub>), perimidine (N<sub>2</sub>), pyridoindole (N<sub>2</sub>); and,

25 C<sub>14</sub> heteroaryl groups (with 3 fused rings) derived from  
acridine (N<sub>1</sub>), xanthene (O<sub>1</sub>), thioxanthene (S<sub>1</sub>), oxanthrene (O<sub>2</sub>),  
phenoxathiin (O<sub>1</sub>S<sub>1</sub>), phenazine (N<sub>2</sub>), phenoxazine (N<sub>1</sub>O<sub>1</sub>),  
phenothiazine (N<sub>1</sub>S<sub>1</sub>), thianthrene (S<sub>2</sub>), phenanthridine (N<sub>1</sub>),  
phenanthroline (N<sub>2</sub>), phenazine (N<sub>2</sub>).

30

Heterocyclic groups (including heteroaryl groups) which have a  
nitrogen ring atom in the form of an -NH- group may be  
N-substituted, that is, as -NR-. For example, pyrrole may be N-  
methyl substituted, to give N-methylpyrrole. Examples of N-  
35 substituents include, but are not limited to C<sub>1-7</sub> alkyl, C<sub>3-20</sub>  
heterocyclyl, C<sub>5-20</sub> carboaryl, C<sub>5-20</sub> heteroaryl and acyl groups.



Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an  $-N=$  group may be substituted in the form of an N-oxide, that is, as  $-N(\rightarrow O)=$  (also denoted  $-N^+(\rightarrow O^-)=$ ). For example, quinoline may be substituted to give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

Cyclic groups may additionally bear one or more oxo ( $=O$ ) groups on ring carbon atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:

C<sub>5</sub>: cyclopentanone, cyclopentenone, cyclopentadienone;

C<sub>6</sub>: cyclohexanone, cyclohexenone, cyclohexadienone;

O<sub>1</sub>: furanone (C<sub>5</sub>), pyrone (C<sub>6</sub>);

N<sub>1</sub>: pyrrolidone (pyrrolidinone) (C<sub>5</sub>), piperidinone (piperidone) (C<sub>6</sub>), piperidinedione (C<sub>6</sub>);

N<sub>2</sub>: imidazolidone (imidazolidinone) (C<sub>5</sub>), pyrazolone (pyrazolinone) (C<sub>5</sub>), piperazinone (C<sub>6</sub>), piperazinedione (C<sub>6</sub>), pyridazinone (C<sub>6</sub>), pyrimidinone (C<sub>6</sub>) (e.g., cytosine),

pyrimidinedione (C<sub>6</sub>) (e.g., thymine, uracil), barbituric acid (C<sub>6</sub>);

N<sub>1</sub>S<sub>1</sub>: thiazolone (C<sub>5</sub>), isothiazolone (C<sub>5</sub>);

N<sub>1</sub>O<sub>1</sub>: oxazolinone (C<sub>5</sub>).

Polycyclic examples of such groups include, but are not limited to, those derived from:

C<sub>9</sub>: indenedione;

C<sub>10</sub>: tetralone, decalone;

C<sub>14</sub>: anthrone, phenanthrone;

N<sub>1</sub>: oxindole (C<sub>9</sub>);

O<sub>1</sub>: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C<sub>10</sub>);

N<sub>1</sub>O<sub>1</sub>: benzoxazolinone (C<sub>9</sub>), benzoxāzolinone (C<sub>10</sub>);

N<sub>2</sub>: quinazolinone (C<sub>10</sub>);

N<sub>4</sub>: purinone (C<sub>9</sub>) (e.g., guanine).

Still more examples of cyclic groups which bear one or more oxo (=O) groups on ring carbon atoms include, but are not limited to, those derived from:

- 5 imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C<sub>5</sub>), maleimide (C<sub>5</sub>), phthalimide, and glutarimide (C<sub>6</sub>);
- lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to,  $\beta$ -propiolactone,  $\gamma$ -butyrolactone,  $\delta$ -valerolactone (2-piperidone), and  $\epsilon$ -caprolactone;
- 10 lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to,  $\beta$ -propiolactam (C<sub>4</sub>),  $\gamma$ -butyrolactam (2-pyrrolidone) (C<sub>5</sub>),  $\delta$ -valerolactam (C<sub>6</sub>), and  $\epsilon$ -caprolactam (C<sub>7</sub>);
- cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone (C<sub>5</sub>);
- 15 cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone (C<sub>5</sub>) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C<sub>6</sub>).

The above alkyl, heterocyclyl, carboaryl and heteroaryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below, unless otherwise stated. Carboaryl and heteroaryl groups may also be substituted by alkoxy groups as defined below.

25

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

- 30 Ether: -OR, wherein R is an ether substituent, for example, a C<sub>1-7</sub> alkyl group (also referred to as a C<sub>1-7</sub> alkoxy group, discussed below), a C<sub>3-20</sub> heterocyclyl group (also referred to as a C<sub>3-20</sub> heterocycliloxy group), or a C<sub>5-20</sub> aryl group (also referred to as a C<sub>5-20</sub> aryloxy group), preferably a C<sub>1-7</sub> alkyl group. The term C<sub>5-20</sub>
- 35 aryl group encompasses both C<sub>5-20</sub> carboaryl and C<sub>5-20</sub> heteroaryl groups.

C<sub>1-7</sub> alkoxy: -OR, wherein R is a C<sub>1-7</sub> alkyl group. Examples of C<sub>1-7</sub> alkoxy groups include, but are not limited to, -OMe (methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and  
5 -O(tBu) (tert-butoxy).

Acetal: -CH(OR<sup>1</sup>)(OR<sup>2</sup>), wherein R<sup>1</sup> and R<sup>2</sup> are independently acetal substituents, for example, a C<sub>1-7</sub> alkyl group, a C<sub>3-20</sub> heterocyclyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group, or, in  
10 the case of a "cyclic" acetal group, R<sup>1</sup> and R<sup>2</sup>, taken together with the two oxygen atoms to which they are attached, and the carbon atoms to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of acetal groups include, but are not limited to, -CH(OMe)<sub>2</sub>, -CH(OEt)<sub>2</sub>, and  
15 -CH(OMe)(OEt).

Hemiacetal: -CH(OH)(OR<sup>1</sup>), wherein R<sup>1</sup> is a hemiacetal substituent, for example, a C<sub>1-7</sub> alkyl group, a C<sub>3-20</sub> heterocyclyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group. Examples of  
20 hemiacetal groups include, but are not limited to, -CH(OH)(OMe) and -CH(OH)(OEt).

Ketal: -CR(OR<sup>1</sup>)(OR<sup>2</sup>), where R<sup>1</sup> and R<sup>2</sup> are as defined for acetals, and R is a ketal substituent other than hydrogen, for example, a  
25 C<sub>1-7</sub> alkyl group, a C<sub>3-20</sub> heterocyclyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group. Examples ketal groups include, but are not limited to, -C(Me)(OMe)<sub>2</sub>, -C(Me)(OEt)<sub>2</sub>, -C(Me)(OMe)(OEt), -C(Et)(OMe)<sub>2</sub>, -C(Et)(OEt)<sub>2</sub>, and -C(Et)(OMe)(OEt).

30 Hemiketal: -CR(OH)(OR<sup>1</sup>), where R<sup>1</sup> is as defined for hemiacetals, and R is a hemiketal substituent other than hydrogen, for example, a C<sub>1-7</sub> alkyl group, a C<sub>3-20</sub> heterocyclyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group. Examples of hemiketal groups include, but are not limited to, -C(Me)(OH)(OMe), -  
35 C(Et)(OH)(OMe), -C(Me)(OH)(OEt), and -C(Et)(OH)(OEt).

Oxo (keto, -one): =O.

Thione (thioketone):  $=S$ .

5 Imino (imine):  $=NR$ , wherein R is an imino substituent, for example, hydrogen,  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group. Examples of ester groups include, but are not limited to,  $=NH$ ,  $=NMe$ ,  $=NEt$ , and  $=NPh$ .

10 Formyl (carbaldehyde, carboxaldehyde):  $-C(=O)H$ .

15 Acyl (keto):  $-C(=O)R$ , wherein R is an acyl substituent, for example, a  $C_{1-7}$  alkyl group (also referred to as  $C_{1-7}$  alkylacyl or  $C_{1-7}$  alkanoyl), a  $C_{3-20}$  heterocyclyl group (also referred to as  $C_{3-20}$  heterocyclylacyl), or a  $C_{5-20}$  aryl group (also referred to as  $C_{5-20}$  arylacyl), preferably a  $C_{1-7}$  alkyl group. Examples of acyl groups include, but are not limited to,  $-C(=O)CH_3$  (acetyl),  $-C(=O)CH_2CH_3$  (propionyl),  $-C(=O)C(CH_3)_3$  (t-butyryl), and  $-C(=O)Ph$  (benzoyl, phenone).

20 Carboxy (carboxylic acid):  $-C(=O)OH$ .

Thiocarboxy (thiocarboxylic acid):  $-C(=S)SH$ .

25 Thiolo-carboxy (thiolo-carboxylic acid):  $-C(=O)SH$ .

Thiono-carboxy (thiono-carboxylic acid):  $-C(=S)OH$ .

Imidic acid:  $-C(=NH)OH$ .

30 Hydroxamic acid:  $-C(=O)NHOH$ .

Ester (carboxylate, carboxylic acid ester, oxycarbonyl):  $-C(=O)OR$ , wherein R is an ester substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of ester groups include,

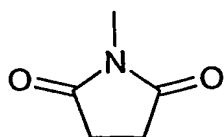
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but are not limited to,  $-C(=O)OCH_3$ ,  $-C(=O)OCH_2CH_3$ ,  $-C(=O)OC(CH_3)_3$ , and  $-C(=O)OPh$ .

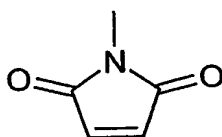
Acyloxy (reverse ester):  $-OC(=O)R$ , wherein R is an acyloxy substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of acyloxy groups include, but are not limited to,  $-OC(=O)CH_3$  (acetoxy),  $-OC(=O)CH_2CH_3$ ,  $-OC(=O)C(CH_3)_3$ ,  $-OC(=O)Ph$ , and  $-OC(=O)CH_2Ph$ .

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide):  $-C(=O)NR^1R^2$ , wherein  $R^1$  and  $R^2$  are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to,  $-C(=O)NH_2$ ,  $-C(=O)NHCH_3$ ,  $-C(=O)N(CH_3)_2$ ,  $-C(=O)NHCH_2CH_3$ , and  $-C(=O)N(CH_2CH_3)_2$ , as well as amido groups in which  $R^1$  and  $R^2$ , together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

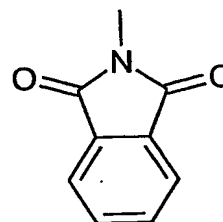
Acylamido (acylamino):  $-NR^1C(=O)R^2$ , wherein  $R^1$  is an amide substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group, and  $R^2$  is an acyl substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group. Examples of acylamide groups include, but are not limited to,  $-NHC(=O)CH_3$ ,  $-NHC(=O)CH_2CH_3$ , and  $-NHC(=O)Ph$ .  $R^1$  and  $R^2$  may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



succinimidyl

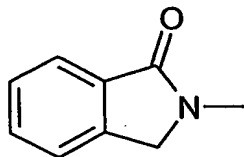


maleimidyl

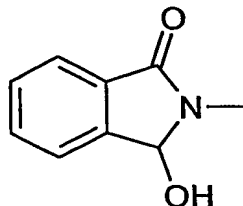


phthalimidyl

or as in 3-hydro-isoindol-1-on-2-yl and 3-hydroxy-3-hydro-isoindol-1-on-2-yl:



3-hydro-isoindol-1-on-2-yl



3-hydroxy-3-hydro-isoindol-1-on-2-yl

Oxalamido:  $-NR^1C(=O)C(=O)NR^2NR^3$ , wherein  $R^2$  and  $R^3$  are

- 5 independently amino substituents, as defined fro amino groups, and  $R^1$  is a oxalamido substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group. Examples of oxalamido groups include, but are not limited to,  $-NHCOC(=O)NH_2$ ,  $-NHCOC(=O)NHMe$ ,  
10  $-NHCOC(=O)NHet$ ,  $-NHCOC(=O)NMe_2$ ,  $-NHCOC(=O)NEt_2$ ,  $-NMeCOC(=O)NH_2$ ,  $-NMeCOC(=O)NHMe$ ,  $-NMeCOC(=O)NHet$ ,  $-NMeCOC(=O)NMe_2$ , and  $-NMeCOC(=O)NEt_2$ .

Thioamido (thiocarbamyl):  $-C(=S)NR^1R^2$ , wherein  $R^1$  and  $R^2$  are independently amino substituents, as defined for amino groups.

- 15 Examples of amido groups include, but are not limited to,  $-C(=S)NH_2$ ,  $-C(=S)NHCH_3$ ,  $-C(=S)N(CH_3)_2$ , and  $-C(=S)NHCH_2CH_3$ .

Ureido:  $-N(R^1)CONR^2R^3$  wherein  $R^2$  and  $R^3$  are independently amino substituents, as defined for amino groups, and  $R^1$  is a ureido substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group. Examples of ureido groups include, but are not limited to,  $-NHCONH_2$ ,  $-NHCONHMe$ ,  $-NHCONHet$ ,  $-NHCONMe_2$ ,  $-NHCONEt_2$ ,  $-NMeCONH_2$ ,  $-NMeCONHMe$ ,  $-NMeCONHet$ ,  $-NMeCONMe_2$ , and  $-NMeCONEt_2$ .

25

Carbamate:  $-NR^1C(=O)OR^2$ , wherein  $R^1$  is an amide substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group, and  $R^2$  is an ester substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$

30

alkyl group. Examples of carbamate groups include, but are not limited to,  $\text{-NHC(=O)OCH}_3$ ,  $\text{-NHC(=O)OCH}_2\text{CH}_3$ , and  $\text{-NHC(=O)OPh}$ .

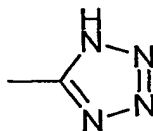
Reverse carbamate:  $\text{-OC(=O)NR}^1\text{R}^2$ , wherein  $\text{R}^1$  and  $\text{R}^2$  are

- 5 independently amino substituents, as defined for amino groups. Examples of reverse carbamate groups include, but are not limited to,  $\text{-OC(=O)NH}_2$ ,  $\text{-OC(=O)NHCH}_2\text{CH}_3$ , and  $\text{-OC(=O)NHPh}$ .

Guanidino:  $\text{-NH-C(=NH)NH}_2$ .

10

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



- 15 Amino:  $\text{-NR}^1\text{R}^2$ , wherein  $\text{R}^1$  and  $\text{R}^2$  are independently amino substituents, for example, hydrogen, a  $\text{C}_{1-7}$  alkyl group (also referred to as  $\text{C}_{1-7}$  alkylamino or di- $\text{C}_{1-7}$  alkylamino), a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably H or a  $\text{C}_{1-7}$  alkyl group, or, in the case of a "cyclic" amino group,  $\text{R}^1$  and  $\text{R}^2$ ,  
20 taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ( $\text{-NH}_2$ ), secondary ( $\text{-NHR}^1$ ), or tertiary ( $\text{-NHR}^1\text{R}^2$ ), and in cationic form, may be quaternary ( $\text{-}^+\text{NR}^1\text{R}^2\text{R}^3$ ). Examples of amino groups include, but are not limited to,  $\text{-NH}_2$ ,  
25  $\text{-NHCH}_3$ ,  $\text{-NHC(CH}_3)_2$ ,  $\text{-N(CH}_3)_2$ ,  $\text{-N(CH}_2\text{CH}_3)_2$ , and  $\text{-NHPh}$ . Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.
- 30 Imino:  $\text{=NR}$ , wherein R is an imino substituent, for example, for example, hydrogen, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably H or a  $\text{C}_{1-7}$  alkyl group. Examples of imino groups include, but are not limited to,  $\text{=NH}$ ,  $\text{=NMe}$ , and  $\text{=NEt}$ .

35

Amidine (amidino):  $-C(=NR)NR_2$ , wherein each R is an amidine substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably H or a  $C_{1-7}$ alkyl group. Examples of amidine groups include, but are not  
5 limited to,  $-C(=NH)NH_2$ ,  $-C(=NH)NMe_2$ , and  $-C(=NMe)NMe_2$ .

Nitro:  $-NO_2$ .

Azido:  $-N_3$ .

10

Cyano (nitrile, carbonitrile):  $-CN$ .

Cyanato:  $-OCN$ .

15 Sulfhydryl (thiol, mercapto):  $-SH$ .

Thioether (sulfide):  $-SR$ , wherein R is a thioether substituent, for example, a  $C_{1-7}$  alkyl group (also referred to as a  $C_{1-7}$  alkylthio group), a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$ alkyl group. Examples of  $C_{1-7}$  alkylthio groups  
20 include, but are not limited to,  $-SCH_3$  and  $-SCH_2CH_3$ .

Sulfine (sulfinyl, sulfoxide):  $-S(=O)R$ , wherein R is a sulfine substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl  
25 group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$ alkyl group. Examples of sulfine groups include, but are not limited to,  $-S(=O)CH_3$  and  $-S(=O)CH_2CH_3$ .

Sulfone (sulfonyl):  $-S(=O)_2R$ , wherein R is a sulfone substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  
30  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$  alkyl group, including, for example, a fluorinated or perfluorinated  $C_{1-7}$  alkyl group. Examples of sulfone groups include, but are not limited to,  $-S(=O)_2CH_3$  (methanesulfonyl, mesyl),  $-S(=O)_2CF_3$  (triflyl),  
35  $-S(=O)_2CH_2CH_3$  (esyl),  $-S(=O)_2C_4F_9$  (nonafllyl),  $-S(=O)_2CH_2CF_3$  (tresyl),  $-S(=O)_2CH_2CH_2NH_2$  (tauryl),  $-S(=O)_2Ph$  (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl



(closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

5 Sulfinic acid (sulfino):  $\text{-S(=O)OH}$ ,  $\text{-SO}_2\text{H}$ .

Sulfonic acid (sulfo):  $\text{-S(=O)}_2\text{OH}$ ,  $\text{-SO}_3\text{H}$ .

10 Sulfinate (sulfinic acid ester):  $\text{-S(=O)OR}$ ; wherein R is a sulfinate substituent, for example, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably a  $\text{C}_{1-7}$  alkyl group. Examples of sulfinate groups include, but are not limited to,  $\text{-S(=O)OCH}_3$  (methoxysulfinyl; methyl sulfinate) and  $\text{-S(=O)OCH}_2\text{CH}_3$  (ethoxysulfinyl; ethyl sulfinate).

15 Sulfonate (sulfonic acid ester):  $\text{-S(=O)}_2\text{OR}$ , wherein R is a sulfonate substituent, for example, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably a  $\text{C}_{1-7}$  alkyl group. Examples of sulfonate groups include, but are not limited to,  $\text{-S(=O)}_2\text{OCH}_3$  (methoxysulfonyl; methyl sulfonate) and  $\text{-S(=O)}_2\text{OCH}_2\text{CH}_3$  (ethoxysulfonyl; ethyl sulfonate).

25 Sulfinyloxy:  $\text{-OS(=O)R}$ , wherein R is a sulfinyloxy substituent, for example, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably a  $\text{C}_{1-7}$  alkyl group. Examples of sulfinyloxy groups include, but are not limited to,  $\text{-OS(=O)CH}_3$  and  $\text{-OS(=O)CH}_2\text{CH}_3$ .

30 Sulfonyloxy:  $\text{-OS(=O)}_2\text{R}$ , wherein R is a sulfonyloxy substituent, for example, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably a  $\text{C}_{1-7}$  alkyl group. Examples of sulfonyloxy groups include, but are not limited to,  $\text{-OS(=O)}_2\text{CH}_3$  (mesylate) and  $\text{-OS(=O)}_2\text{CH}_2\text{CH}_3$  (esylate).

35 Sulfate:  $\text{-OS(=O)}_2\text{OR}$ ; wherein R is a sulfate substituent, for example, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably a  $\text{C}_{1-7}$  alkyl group. Examples of sulfate

groups include, but are not limited to,  $-\text{OS}(=\text{O})_2\text{OCH}_3$  and  $-\text{SO}(=\text{O})_2\text{OCH}_2\text{CH}_3$ .

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide):

- 5  $-\text{S}(=\text{O})\text{NR}^1\text{R}^2$ , wherein  $\text{R}^1$  and  $\text{R}^2$  are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to,  $-\text{S}(=\text{O})\text{NH}_2$ ,  $-\text{S}(=\text{O})\text{NH}(\text{CH}_3)$ ,  $-\text{S}(=\text{O})\text{N}(\text{CH}_3)_2$ ,  $-\text{S}(=\text{O})\text{NH}(\text{CH}_2\text{CH}_3)$ ,  $-\text{S}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$ , and  $-\text{S}(=\text{O})\text{NHPh}$ .

- 10 Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide):

- $-\text{S}(=\text{O})_2\text{NR}^1\text{R}^2$ , wherein  $\text{R}^1$  and  $\text{R}^2$  are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to,  $-\text{S}(=\text{O})_2\text{NH}_2$ ,  $-\text{S}(=\text{O})_2\text{NH}(\text{CH}_3)$ ,  $-\text{S}(=\text{O})_2\text{N}(\text{CH}_3)_2$ ,  $-\text{S}(=\text{O})_2\text{NH}(\text{CH}_2\text{CH}_3)$ ,  $-\text{S}(=\text{O})_2\text{N}(\text{CH}_2\text{CH}_3)_2$ , and  $-\text{S}(=\text{O})_2\text{NHPh}$ .
- 15

Sulfamino:  $-\text{NR}^1\text{S}(=\text{O})_2\text{OH}$ , wherein  $\text{R}^1$  is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to,  $-\text{NHS}(=\text{O})_2\text{OH}$  and  $-\text{N}(\text{CH}_3)\text{S}(=\text{O})_2\text{OH}$ .

- 20 Sulfonamino:  $-\text{NR}^1\text{S}(=\text{O})_2\text{R}$ , wherein  $\text{R}^1$  is an amino substituent, as defined for amino groups, and  $\text{R}$  is a sulfonamino substituent, for example, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably a  $\text{C}_{1-7}$  alkyl group. Examples of sulfonamino groups include, but are not limited to,  $-\text{NHS}(=\text{O})_2\text{CH}_3$  and  $-\text{N}(\text{CH}_3)\text{S}(=\text{O})_2\text{C}_6\text{H}_5$ .
- 25

- Sulfonbisamino:  $-\text{N}(\text{S}(=\text{O})_2\text{R})_2$ , wherein  $\text{R}$  is a sulfonamino substituent, as defined for sulfonamino groups. Examples of sulfonbisamino groups include, but are not limited to,  $-\text{N}(\text{S}(=\text{O})_2\text{CH}_3)_2$  and  $-\text{N}(\text{S}(=\text{O})_2\text{C}_6\text{H}_5)_2$ .
- 30

- Sulfinamino:  $-\text{NR}^1\text{S}(=\text{O})\text{R}$ , wherein  $\text{R}^1$  is an amino substituent, as defined for amino groups, and  $\text{R}$  is a sulfinamino substituent, for example, a  $\text{C}_{1-7}$  alkyl group, a  $\text{C}_{3-20}$  heterocyclyl group, or a  $\text{C}_{5-20}$  aryl group, preferably a  $\text{C}_{1-7}$  alkyl group. Examples of sulfinamino
- 35

groups include, but are not limited to,  $\text{-NHS(=O)CH}_3$  and  $\text{-N(CH}_3\text{)S(=O)C}_6\text{H}_5$ .

#### Further groups

- 5 Alkoxylyene: The term "alkoxylyene" as used herein, pertains to a bidentate group which may be a substituent of an aryl group. It bonds to adjacent atoms of the aryl group, and may one or two carbon atoms in the chain between the oxygen atoms, as thus has the structure  $\text{-O(CH}_2\text{)}_n\text{O-}$ , where  $n$  is either 1 or 2. The carbon  
10 atoms may bear any of the substituents listed above.

#### Includes Other Forms

- Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these  
15 substituents. For example, a reference to carboxylic acid ( $\text{-COOH}$ ) also includes the anionic (carboxylate) form ( $\text{-COO}^-$ ), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ( $\text{-N}^+\text{HR}^1\text{R}^2$ ), a salt or solvate of the amino group, for  
20 example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ( $\text{-O}^-$ ), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

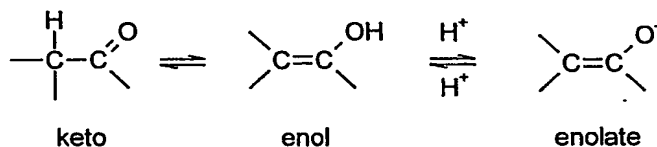
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#### Isomers, Salts, Solvates, Protected Forms, and Prodrugs

- Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not  
30 limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r-forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms;  $\alpha$ - and  $\beta$ -forms; axial and equatorial forms; boat-, chair-,  
35 twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group,  $-OCH_3$ , is not to be construed as a reference to its structural isomer, a hydroxymethyl group,  $-CH_2OH$ . Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g.,  $C_{1-7}$ alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including  $^1\text{H}$ ,  $^2\text{H}$  (D), and  $^3\text{H}$  (T); C may be in any isotopic form, including  $^{12}\text{C}$ ,  $^{13}\text{C}$ , and  $^{14}\text{C}$ ; O may be in any isotopic form, including  $^{16}\text{O}$  and  $^{18}\text{O}$ ; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Isomeric forms substantially free, i.e. associated with less than 5%, preferably less than 2%, in particular less than 1%, of the other isomeric form are also envisaged. Methods for the preparation (e.g., asymmetric

synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

5

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

- 10 It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 15 1-19.

- For example, if the compound is anionic, or has a functional group which may be anionic (e.g.,  $\text{-COOH}$  may be  $\text{-COO}^-$ ), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as  $\text{Na}^+$  and  $\text{K}^+$ , alkaline earth cations such as  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ , and other cations such as  $\text{Al}^{3+}$ . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e.,  $\text{NH}_4^+$ ) and substituted ammonium ions (e.g.,  $\text{NH}_3\text{R}^+$ ,  $\text{NH}_2\text{R}_2^+$ ,  $\text{NHR}_3^+$ ,  $\text{NR}_4^+$ ).  
20 Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, 25 such as lysine and arginine. An example of a common quaternary ammonium ion is  $\text{N}(\text{CH}_3)_4^+$ .  
30

- If the compound is cationic, or has a functional group which may be cationic (e.g.,  $\text{-NH}_2$  may be  $\text{-NH}_3^+$ ), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions 35 include, but are not limited to, those derived from the following

inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

5 Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids:  
2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic,  
10 isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric  
15 organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or  
20 handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-  
25 hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the  
30 conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render  
35 unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected

or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH<sub>3</sub>, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH(OR)<sub>2</sub>) or ketal (R<sub>2</sub>C(OR)<sub>2</sub>), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C(OR)<sub>2</sub>), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a

methyl amide ( $-\text{NHCO}-\text{CH}_3$ ); a benzyloxy amide ( $-\text{NHCO}-\text{OCH}_2\text{C}_6\text{H}_5$ ,  $-\text{NH}-\text{Cbz}$ ); as a t-butoxy amide ( $-\text{NHCO}-\text{OC}(\text{CH}_3)_3$ ,  $-\text{NH}-\text{Boc}$ ); a 2-biphenyl-2-propoxy amide ( $-\text{NHCO}-\text{OC}(\text{CH}_3)_2\text{C}_6\text{H}_4\text{C}_6\text{H}_5$ ,  $-\text{NH}-\text{Bpoc}$ ), as a 9-fluorenylmethoxy amide ( $-\text{NH}-\text{Fmoc}$ ), as a 6-nitroveratryloxy amide ( $-\text{NH}-\text{Nvoc}$ ), as a 2-trimethylsilylethyloxy amide ( $-\text{NH}-\text{Teoc}$ ), as a 2,2,2-trichloroethyloxy amide ( $-\text{NH}-\text{Troc}$ ), as an allyloxy amide ( $-\text{NH}-\text{Alloc}$ ), as a 2(-phenylsulphonyl)ethyloxy amide ( $-\text{NH}-\text{Psec}$ ); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical ( $>\text{N}-\text{O}\cdot$ ).

10

For example, a carboxylic acid group may be protected as an ester for example, as: an  $\text{C}_{1-7}$  alkyl ester (e.g., a methyl ester; a t-butyl ester); a  $\text{C}_{1-7}$  haloalkyl ester (e.g., a  $\text{C}_{1-7}$  trihaloalkyl ester); a tri $\text{C}_{1-7}$  alkylsilyl- $\text{C}_{1-7}$  alkyl ester; or a  $\text{C}_{5-20}$  aryl- $\text{C}_{1-7}$  alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

15

For example, a thiol group may be protected as a thioether ( $-\text{SR}$ ), for example, as: a benzyl thioether; an acetamidomethyl ether ( $-\text{S}-\text{CH}_2\text{NHC}(=\text{O})\text{CH}_3$ ).

20

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which, when metabolised (e.g., in vivo), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties.

25

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester).

During metabolism, the ester group ( $-\text{C}(=\text{O})\text{OR}$ ) is cleaved to yield the active drug. Such esters may be formed by

35

esterification, for example, of any of the carboxylic acid groups ( $-\text{C}(=\text{O})\text{OH}$ ) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.



Examples of such metabolically labile esters include those of the formula  $-C(=O)OR$  wherein R is:

$C_{1-7}$ alkyl

5 (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);

$C_{1-7}$ aminoalkyl

(e.g., aminoethyl; 2-(N,N-diethylamino)ethyl;

2-(4-morpholino)ethyl); and

acyloxy- $C_{1-7}$ alkyl

10 (e.g., acyloxymethyl;

acyloxyethyl;

pivaloyloxymethyl;

acetoxymethyl;

1-acetoxyethyl;

15 1-(1-methoxy-1-methyl)ethyl-carbonyloxyethyl;

1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl;

1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl;

1-cyclohexyl-carbonyloxyethyl;

cyclohexyloxy-carbonyloxymethyl;

20 1-cyclohexyloxy-carbonyloxyethyl;

(4-tetrahydropyranyloxy) carbonyloxymethyl;

1-(4-tetrahydropyranyloxy) carbonyloxyethyl;

(4-tetrahydropyranyl) carbonyloxymethyl; and

1-(4-tetrahydropyranyl) carbonyloxyethyl).

25

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

30

#### Preferences

The following preferences apply to each aspect of the present invention, and preferred compounds may be different for different aspects. The following preferences for each group may be combined in any way with preferences for other groups.

35

-X=Y-

It is preferred that -X=Y- is  $-CR^2=N-$ , i.e. that the compounds are of formula **Ib**.

5

$R^5$

$R^5$  is preferably selected from  $R^{5'}$ , halo,  $NHR^{5'}$ ,  $OR^{5'}$ ,  $SR^{5'}$ , wherein  $R^{5'}$  is H or  $C_{1-3}$  alkyl (optionally substituted by halo,  $NH_2$ , OH, SH). Of these groups, H,  $NHR^{5'}$  (more preferably  $NH_2$ ), OH, SH and halo (more preferably F or Cl) are more preferred, with H and  $NH_2$  being the most preferred. If the compound is a pyridine then preferably  $R^5$  is  $NH_2$ , and if the compound is a pyrazine preferably  $R^5$  is H.

15

$R^1$

$R^1$  is preferably selected from H,  $NRR'$ ,  $NHC(=O)R$ ,  $NHC(=O)NRR'$ , and  $NH_2SO_2R$ , and more preferably from H and  $NRR'$ , or from H and  $NH_2$ .  $R^1$  is most preferably H.

20

$R^2$  and  $R^3$

$R^2$  and  $R^3$  (where present) are preferably independently selected from H, halo, amino, hydroxy and thio, and more preferably from H and halo. If only one of  $R^2$  and  $R^3$  is a substituent, then  $R^2$  is the preferred substituent.

25

$R^4$

$R^4$  is preferably an optionally substituted  $C_{5-10}$  aryl group, more preferably either a  $C_{5-10}$  carboaryl group or a  $C_{5-10}$  heteroaryl group having one or two nitrogen ring atoms, for example, naphthyl, phenyl, indole, quinoline, isoquinoline, tetrahydroquinoline, tetrahydroisoquinoline, pyridine, phthalazine, tetrahydrophthalazine, quinazoline and tetrahydroquinazoline.

35

In one embodiment  $R^4$  is an optionally substituted  $C_{5-10}$  carboaryl group, and more preferably an optionally substituted phenyl or naphthyl group.

If R<sup>4</sup> is a naphthyl group it is preferably unsubstituted, and may be in any configuration, with naphth-1-yl being preferred.

- 5 If R<sup>4</sup> is a phenyl group, then it is preferably substituted, more preferably with one or two substituents.

10 These are preferably selected from halo (more preferably F and Cl), ether (more preferably C<sub>1-7</sub> alkoxy, and in particular -OMe, and arylalkoxy, and in particular benzyloxy), C<sub>1-7</sub> alkyl (more preferably C<sub>1-4</sub> alkyl, and in particular -Me, and -CF<sub>3</sub>), C<sub>5-20</sub> aryl groups (more preferably C<sub>5-10</sub> carboaryl or heteroaryl groups), amido, acylamido, ureido, carbamate and reverse carbamate. Alkoxy groups linked to adjacent atoms are also preferred.

15 In particular amido, acylamido, ureido, carbamate and reverse carbamate groups are preferred, optionally in combination with a halo group, which is preferably para to the former groups. The former groups are preferably in the 3-position.

20 If there is one substituent, the ortho and meta positions are preferred, with the meta position being the most preferred. If two substituents are present, it may be preferred that neither is in the para position, unless one is F, when this is preferred to be in the para position.

25 In another embodiment, R<sup>4</sup> is preferably a bicyclic aryl group, where the second ring can be aromatic or non-aromatic (partially or fully saturated). Such groups include naphthyl, indole, oxindole, quinoline, isoquinoline, tetrahydroquinoline and tetrahydroisoquinoline.

30 The class of compounds wherein R<sup>1</sup> is selected from H, NRR', NHC(=O)R, NHC(=O)NRR', NH<sub>2</sub>SO<sub>2</sub>R, and C(=O)NRR', where R and R' are independently selected from H and C<sub>1-4</sub> alkyl, and are optionally substituted by OH, NH<sub>2</sub>, C<sub>5-20</sub> carboaryl, and C<sub>5-20</sub> heteroaryl, or may together form, with the nitrogen atom to which they are

attached, an optionally substituted nitrogen containing C<sub>5-7</sub> heterocyclyl group;

R<sup>5</sup> is selected from H and NH<sub>2</sub>;

R<sup>4</sup> is phenyl, with an optional 5-halo group and a 3-amido, ureido,

5 carbamate, or reverse carbamate group bearing a H, optionally substituted C<sub>5-20</sub> carboaryl or optionally substituted C<sub>5-20</sub> heteroaryl group, are in some embodiments preferably excluded from the aspects of the present invention. These compounds are described in co-pending applications GB0215383.1 and US  
10 60/393,121.

#### Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl  
15 (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

20 For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et<sub>2</sub>O), acetic acid (AcOH),  
25 dichloromethane (methylene chloride, DCM), acetonitrile (ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

#### Synthesis Routes

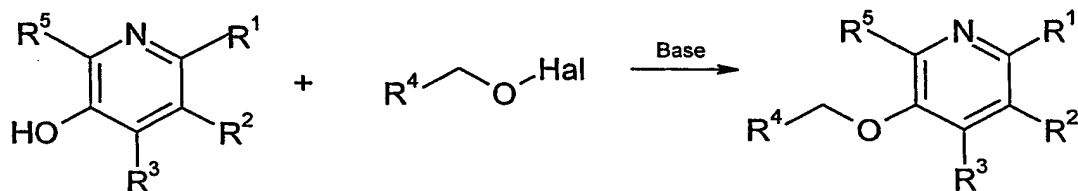
30 Several methods for the chemical synthesis of compounds of the present invention are described herein. These methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds within the scope of the present invention. The amounts of reactants given are for guidance.

35 Descriptions of general laboratory methods and procedures, useful for the preparation of the compounds of the present invention, are described in Vogel's Textbook of Practical Organic Chemistry.

(5<sup>th</sup> edition, Ed. Furniss, B. S., Hannaford, A.J., Smith, P.W.G., Tatchell, A.R., Longmann, UK). Methods for the synthesis of pyridine and pyrazine containing molecules in particular are described in Heterocyclic Chemistry, Joule, J.A., Mills, R., and Smith, G.F., Chapman & Hall, London.

#### General routes

The key step in the synthesis of compounds of the present invention is the joining of the pyridine/pyrazine ring to the C<sub>5-20</sub> aryl group with the intervening -O-CH<sub>2</sub>- linkage. As illustrated below, with respect to the pyridine molecule, this is most conveniently achieved by reacting a 3-hydroxy pyridine (or pyrazine) with a halomethyl aryl compound, under basic conditions:



The 3 hydroxy starting material is generally commercially available. The substituents (R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>5</sup>) may be in place in the starting material, having been already introduced using known methods, or may be introduced later in the synthesis, as appropriate. Depending on their structure, protection may be needed to carry out the above step.

The halomethyl aryl compounds may be commercially available or readily synthesised using known techniques. One particular technique for deriving these compounds starts from the corresponding aryl carboxylic acid, which is first reduced, for example, using sodium borohydride, followed by halo-dehalogenation, achieved, for example, by the use of triphenyl phosphine.

If the aryl group (R<sup>4</sup>) bears substituents, then these may either be in place at the beginning of the synthesis, or can be added at

any appropriate stage. In particular, certain substituents on the aryl group can be modified, using known reactions.

*Detailed routes*

5  $R^1$

When  $R^1$  is  $-NRR'$ , one possible method of introducing this substituent is to synthesise the desired compound with  $R^1=F$ , and then carry out direct substitution with  $HNRR'$ .

10 When  $R^1$  is  $-C(=O)NRR'$ , the desired product can be synthesised with  $R^1=-C(=O)OH$ , followed by addition of  $HNRR'$ , using conventional means to aid amide bond formation (see above).

15 When  $R^1$  is  $-NHC(=O)NRR'$ , the desired product can be synthesised with  $R^1=-C(=O)OH$ , which can then be converted to  $-C(=O)-N_3^-$ , using, for example thionyl chloride followed by sodium azide, followed by heating to undergo a Curtius rearrangement to the corresponding isocyanate, which then can undergo addition of  $HNRR'$  to form the desired final product.

20

The isocyanate can also be trapped using tert-butanol to yield a tert-butyl protected carbamic acid, which then undergo base mediated substitution of an appropriate halo-compound ( $Hal-R$ ), to provide an alternative route to compounds where  $R^1$  is  $NHR$ .

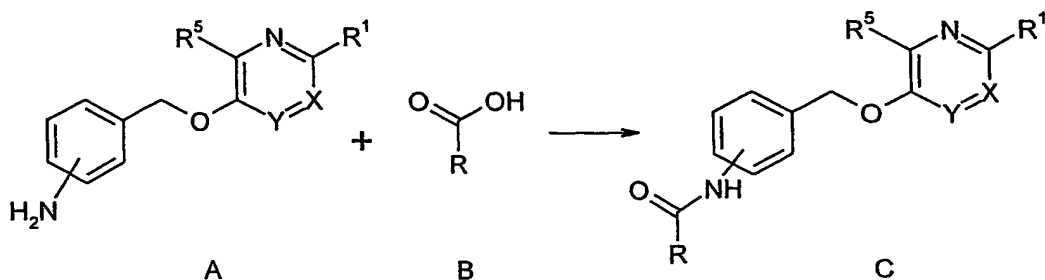
25

When  $R^1$  is  $-NHSO_2R$ , the desired product can be synthesised using the methods described in *J. Med. Chem.*, **1991**, 34(4), 1356-1362, JP 57-038777 and *J. Het. Chem.*, **1980**, 17(1), 11-16.

30 When  $R^1$  is  $-NH-C(=O)-R$ , the desired product can be derived from compounds where  $R^1=NH_2$ , by reaction with  $R-C(=O)OH$ , or an activated version thereof, for example  $R-C(=O)Cl$ .

Derivatising  $R^4$  (illustrated for  $R^4$  = phenyl)

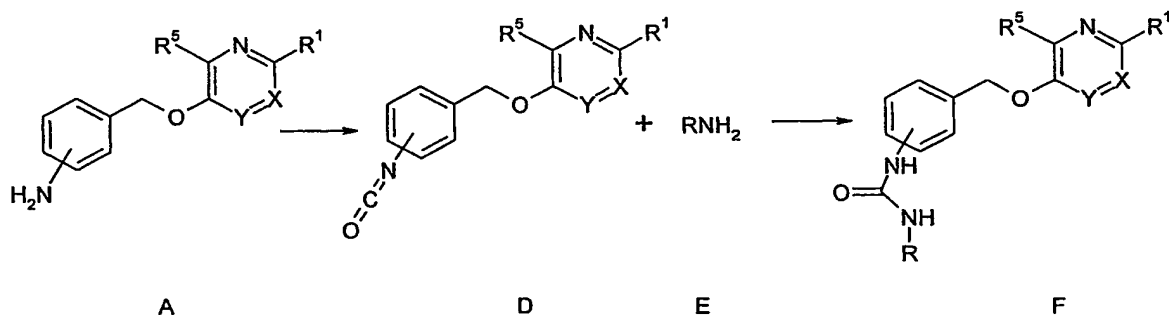
35  $-NH_2$  to  $-NH-C(=O)-R$



Scheme 1

Where it is desired to derivatise  $-\text{NH}_2$  to  $-\text{NH}-\text{C}(=\text{O})-\text{R}$ , the desired compound (C) is made by the reaction between the appropriate phenylamine (A) and the aromatic acid (B), or formic acid (where R is H). Due to the relative unreactivity of the phenyl amine, this reaction is usually carried out with the aid of an activator or promoter. Activation of the acid can be achieved by converting it into the corresponding acid chloride, for example, by using oxalyl chloride. An alternative method employs amide bond forming promoters, 1[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 7-aza-1-hydroxybenzotriazole (HOAt) or 1-hydroxy benzotriazole (HOBt).

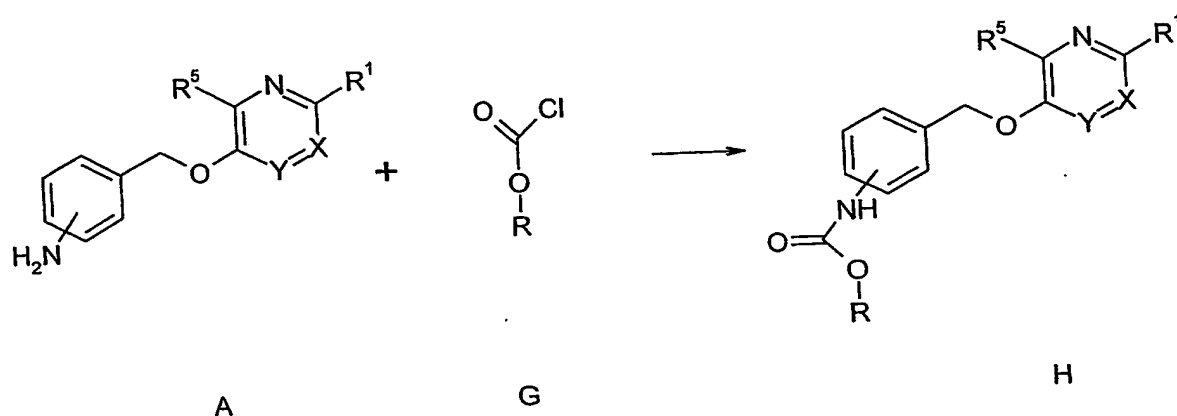
$-\text{NH}_2$  to  $-\text{NH}-\text{C}(=\text{O})-\text{NH}-\text{R}$



Scheme 2

- Where it is desired to derivatise  $-NH_2$  to  $-NH-C(=O)-NH-R$ , the desired compound (F) can be synthesised by the conversion of the appropriate phenylamine (A) to the corresponding isocyanate (D), followed by addition of the appropriate aromatic amine (E), or ammonium hydroxide (where  $R=H$ ) without the need for isolation of the isocyanate (D).

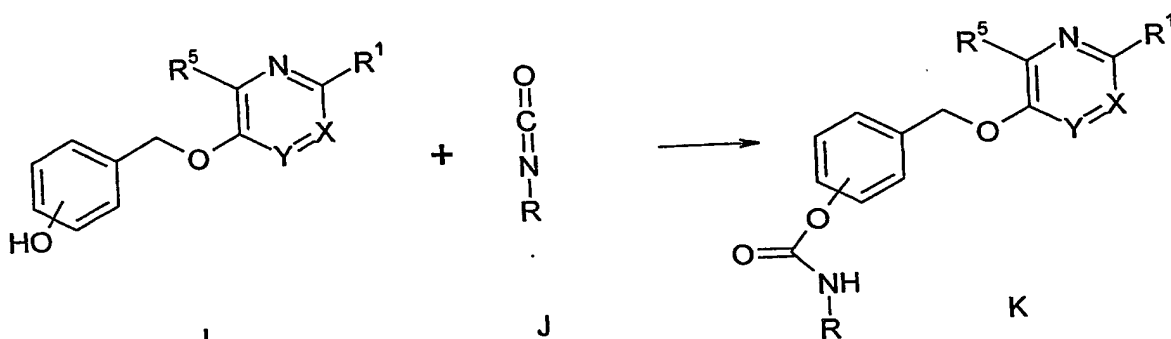
$-NH_2$  to  $-NH-C(=O)-O-R$



Scheme 3

- Where it is desired to derivatise  $-NH_2$  to  $-NH-C(=O)-O-R$ , the desired compound (H) can be synthesised by the addition of the appropriate aromatic chloroformate (G) to the appropriate phenylamine (A).

$-OH$  to  $-O-C(=O)-NH-R$

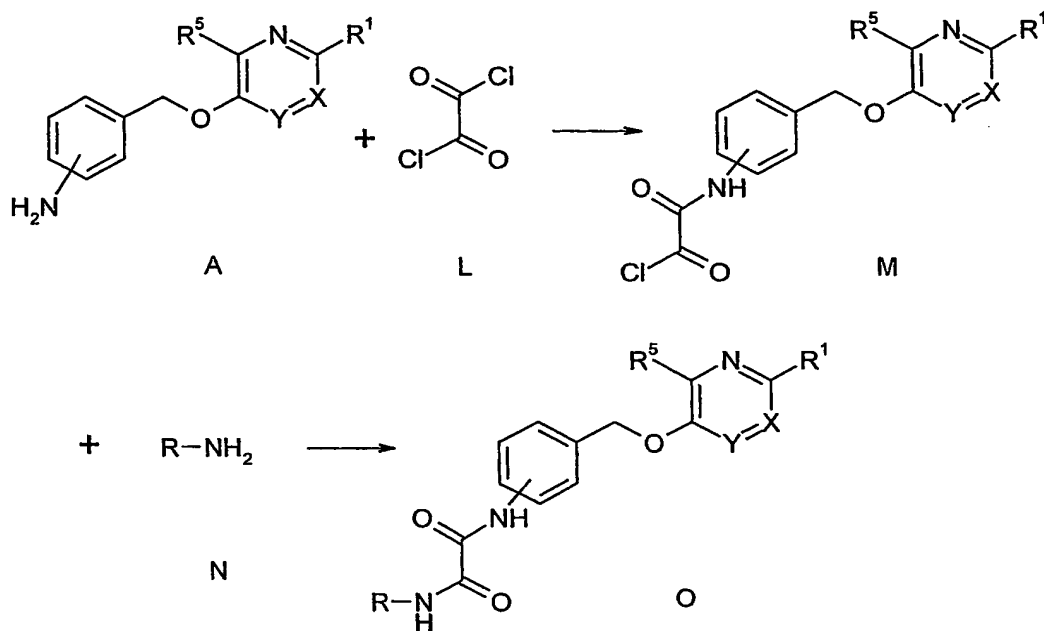




Scheme 4

The desired compound (K) is made by the base mediated reaction between the appropriate phenol and the aromatic isocyanate (J), or  
5 TMS isocyanate (where R is H). An appropriate base would be triethylamine.

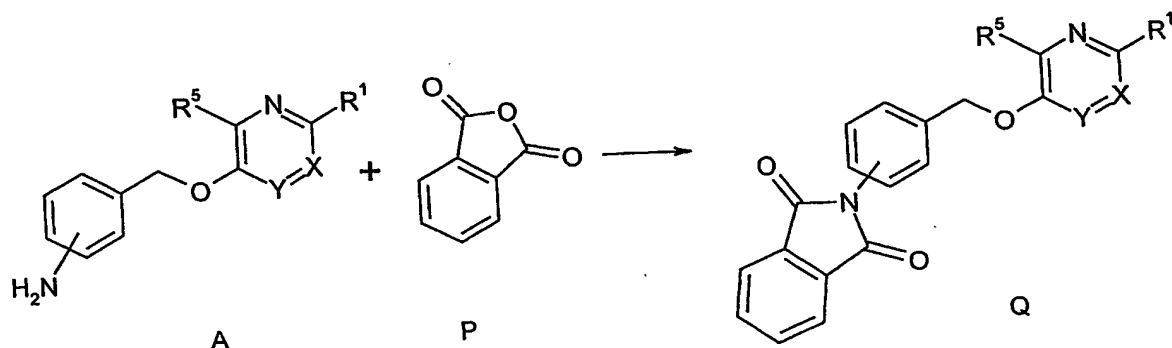
-NH<sub>2</sub> to -NH-C(=O)-C(=O)-NH-R



Scheme 5

Where it is desired to derivatise -NH<sub>2</sub> to -NH-C(=O)-C(=O)-NH-R, the desired compound (O) is made via the intermediate M without isolation. The appropriate phenylamine (A) is first reacted with  
15 oxalyl chloride, followed by the appropriate amine to give the desired oxalamide (O).

-NH<sub>2</sub> to -phthalimidyl



Scheme 6

- 5 Where it is desired to derivatise -NH<sub>2</sub> to -phthalimidyl, the desired compound (Q) is made by reacting phthalic anhydride with the appropriate phenylamine (A).

#### Protection

- 10 In the above routes, groups sensitive to the reaction condition can be appropriately protected to avoid side products being formed. For example, in the routes illustrated above, if one of R<sup>1</sup> to R<sup>5</sup> is -OH or -SH, and alkylation with an electrophilic reagent onto HX or Q might be expected to also undesirably
- 15 substitute these groups, protecting groups for -OH and -SH can be employed (see above discussion of protecting groups).

Embodiments of the invention will now be described by way of example with reference to the drawings, in which:

- 20 Figure 1 illustrates compounds of the invention;  
Figure 2 illustrates further compounds of the invention.

#### Use of Compounds of the Invention

- 25 The present invention provides active compounds, specifically, active pyridine and pyrazine derivatives as defined in the first aspect.

- The term "active," as used herein, pertains to compounds which are capable of inhibiting p38 MAP kinase activity, and
- 30 specifically includes both compounds with intrinsic activity

(drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

One of ordinary skill in the art is readily able to determine whether or not a candidate inhibits p38 MAP kinase activity. For example, an assay which may conveniently be used in order to assess the inhibition of p38 MAP kinase activity offered by a particular compound is described in the examples below.

The present invention further provides a method of inhibiting p38 MAP kinase activity in a cell, comprising contacting said cell with an effective amount of an active compound, preferably in the form of a pharmaceutically acceptable composition. Such a method may be practised *in vitro* or *in vivo*.

The invention further provides active compounds for use in a method of treatment of the human or animal body. Such a method may comprise administering to such a subject a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

The term "treatment" as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

The term "therapeutically-effective amount" as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

The invention further provides the use of an active compound for the manufacture of a medicament, for example, for the treatment of a condition ameliorated by the inhibition of p38 MAP kinase.

The invention further provides a method of treatment of the human or animal body, the method comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

Active compounds may also be used as part of an in vitro assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

#### 25 Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal,

subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot, for example, subcutaneously or intramuscularly.

- 5 The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g. a guinea pig, a hamster, a rat, a mouse), murine (e.g. a mouse), canine (e.g. a dog), feline (e.g. a cat), equine (e.g. a horse), a primate, simian (e.g. a monkey or ape), a monkey (e.g. marmoset, baboon), an ape (e.g. gorilla,  
10 chimpanzee, orang-utan, gibbon), or a human.

#### Formulations

- While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical  
15 composition (e.g. formulation) comprising at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the  
20 art and optionally other therapeutic or prophylactic agents.

- Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one  
25 active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilizers, or other materials, as described herein.

- The term "pharmaceutically acceptable" as used herein pertains to  
30 compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable  
35 benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa.,  
5 1990.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into  
10 association the active compound with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then if necessary  
15 shaping the product.

Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, lozenges, granules, powders, capsules, cachets, pills, ampoules,  
20 suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils, boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g. by ingestion)  
25 may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an  
30 electuary; or as a paste.

A tablet may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable  
35 machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g. povidone, gelatin, acacia, sorbitol, tragacanth,

hydroxypropylmethyl cellulose); fillers or diluents (e.g. lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc, silica); disintegrants (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g. sodium lauryl sulfate); and preservatives (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid). Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g. transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include lozenges comprising the active compound in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active compound in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active compound in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for administration by inhalation include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil.



Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such

carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g. by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the solution is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

#### Dosage

It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of

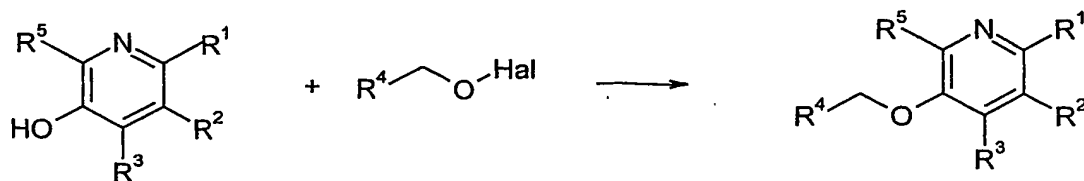
administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration *in vivo* can be effected in one dose, continuously or intermittently (e.g. in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

In general, a suitable dose of the active compound is in the range of about 100 pg to about 10 mg, more preferably 10 ng to 1 mg, per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

### EXAMPLES

#### **Example 1**



A mixture of the appropriate starting material (a 3 hydroxy pyridine - generally commercially available) (2.00 mmol), the appropriate halo compound (2.20 mmol) and Adogen™ 464 (1 drop) in aqueous 40% NaOH solution (2 ml) and dichloromethane (2 ml) is stirred at room temperature for 19 hours. The dichloromethane is separated and the aqueous layer diluted with water (10 ml) and then extracted with dichloromethane (3 x 25 ml). The organic extracts are combined, dried ( $K_2CO_3$ ), filtered and concentrated. Recrystallisation from hexane/dichloromethane or purification using Flash chromatography gives the desired product.

*From 2-amino-3-hydroxypyridine*

2-amino-3-benzyloxy pyridine (1) : from benzyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 4.70 (2H, br s), 5.07 (2H, s), 6.59 (1H, dd, J 8, 5), 6.96 (1H, dd, J 8, 1.5), 7.40 (5H, m), 7.68 (1H, dd, J 5, 1.5).

2-amino-3-(2-fluorobenzyloxy)pyridine (3) : from 2-fluorobenzyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 4.66 (2H, br s), 5.13 (2H, s), 6.61 (1H, dd, J 7.5, 5), 7.01 (1H, dd, J 7.5, 1.5), 7.11 (1H, ddd, J 10, 7.5, 1), 7.17 (1H, td, J 7.5, 1), 7.34 (1H, m), 7.44 (1H, tm, J 7.5), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(4-fluorobenzyloxy)pyridine (4) : from 4-fluorobenzyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 4.67 (2H, br s), 5.02 (2H, s), 6.59 (1H, dd, J 8, 5), 6.95 (1H, dd, J 8, 1.5), 7.08 (2H, t, J 9), 7.39 (2H, dd, J 9, 5), 7.68 (1H, dd, J 5, 1.5).

2-amino-3-(1-naphthylmethyloxy)pyridine (5) : from 1-naphthylmethyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 4.63 (2H, br s), 5.49 (2H, s), 6.64 (1H, dd, J 8, 5), 7.12 (1H, dd, J 8, 1.5), 7.48 (2H, dd, J 8, 7), 7.55 (2H, m), 7.71 (1H, dd, J 5, 1.5), 7.90 (2H, m), 8.03 (1H, m).

2-amino-3-(2-methoxybenzyloxy)pyridine (6) : from 2-methoxybenzyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 3.87 (3H, s), 4.70 (2H, br s), 5.11 (2H, s), 6.59 (1H, dd, J 8, 5), 6.93 (1H, d, J 8), 6.99 (2H, m),

7.32 (1H, m), 7.39 (1H, d, J 7), 7.67 (1H, dd, J 5, 1.5).

2-amino-3-(2-chlorobenzyloxy)pyridine (8) : from 2-chlorobenzyl  
chloride;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 4.70 (2H, br s), 5.17 (2H, s), 6.59  
5 (1H, dd, J 7.5, 5), 6.96 (1H, dd, J 7.5, 1.5), 7.28 (2H, m), 7.41  
(1H, m), 7.47 (1H, m), 7.68 (1H, dd, J 5, 1.5).

2-amino-3-(3-chlorobenzyloxy)pyridine (9) : from 3-chlorobenzyl  
chloride;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 4.69 (2H, br s), 5.04 (2H, s), 6.59  
10 (1H, dd, J 7.5, 5), 6.93 (1H, dd, J 7.5, 1.5), 7.31 (3H, m), 7.42  
(1H, m), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(2,3-difluorobenzyloxy)pyridine (12) : from 2,3-  
difluorobenzyl chloride;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 4.67 (2H, br s), 5.14  
15 (2H, s), 6.60 (1H, dd, J 7.5, 5), 6.98 (1H, dd, J 7.5, 1.5), 7.10  
(1H, m), 7.15 (1H, m), 7.20 (1H, m), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(2,4-difluorobenzyloxy)pyridine (13) : from 2,4-  
difluorobenzyl chloride;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 4.64 (2H, br s), 5.07  
20 (2H, s), 6.60 (1H, dd, J 8, 5), 6.87 (2H, m), 6.98 (1H, dd, J 8,  
1.5), 7.41 (1H, td, J 8.5, 6.5), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(3,4-difluorobenzyloxy)pyridine (14) : from 3,4-  
difluorobenzyl chloride;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 4.66 (2H, br s), 5.00  
25 (2H, s), 6.58 (1H, dd, J 8, 5), 6.91 (1H, dd, J 8, 1.5), 7.18  
(3H, m), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(2,4-dichlorobenzyloxy)pyridine (15) : from 2,4-  
dichlorobenzyl chloride;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 4.68 (2H, br s), 5.13  
30 (2H, s), 6.59 (1H, dd, J 8, 5), 6.93 (1H, dd, J 8, 1.5), 7.27  
(1H, dd, J 8, 2), 7.40 (1H, d, J 8), 7.43 (1H, d, J 2), 7.69 (1H,  
dd, J 5, 1.5).

2-amino-3-(4-chloro-3-fluorobenzyloxy)pyridine (16) : from 4-  
35 chloro-3-fluorobenzyl chloride;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 4.68 (2H, br  
s), 5.12 (2H, s), 6.60 (1H, dd, J 8, 5), 6.95 (1H, dd, J 8, 1.5),

7.01 (1H, J td, 8.5, 2.5), 7.17 (1H, dd, J 8.5, 2.5), 7.44 (1H, dd, J 8.5, 6), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(2-chloro-4,5-(methylenedioxy)benzyloxy)pyridine (18) :

5 from 2-chloro-4,5-(methylenedioxy)benzyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 4.67 (2H, br s), 5.06 (2H, s), 5.98 (2H, s), 6.59 (1H, dd, J 8, 5), 6.87 (1H, s), 6.91 (1H, s), 6.94 (1H, dd, J 8, 1.5), 7.68 (1H, dd, J 5, 1.5).

10 From 3-hydroxypyridine

3-Benzyloxy pyridine (7) : from benzyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 5.11 (2H, s), 7.21 (1H, ddd, J 8.5, 4.5, 1), 7.25 (1H, ddd, J 8.5, 3, 1.5), 7.39 (5H, m), 8.23 (1H, dd, J 4.5, 1.5), 8.40 (1H, d, J 3).

15

3-(1-Naphthylmethyloxy)pyridine (11) : from 1-naphthylmethyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 5.55 (2H, s), 7.24 (1H, ddd, J 8.5, 4.5, 0.5), 7.34 (1H, ddd, J 8.5, 3, 1.5), 7.54 (4H, m), 7.89 (2H, m), 8.04 (1H, m), 8.26 (1H, dd, J 4.5, 1.5), 8.47 (1H, d, J 3).

20

From 2-chloro-3-hydroxypyridine

3-Benzyloxy-2-chloropyridine (10) : from benzyl chloride;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 5.19 (2H, s), 7.16 (1H, dd, J 8.0, 4.5), 7.22 (1H, dd, J 8.0, 1.5), 7.32-7.46 (5H, m), 8.00 (1H, dd, J 4.5, 1.5).

25

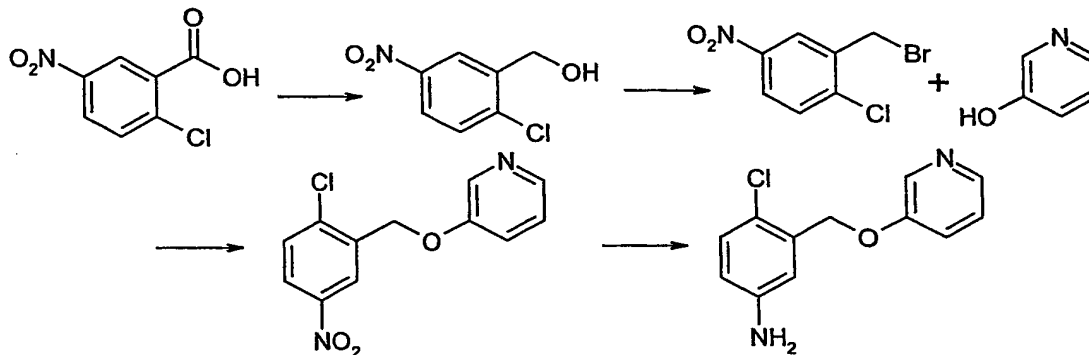
The following compounds were made by analogous methods:

2; 17 - MS(ES): m/e 229 (M+H); 19; 20 - MS(ES): m/e 277 (M+H);  
21; 22; 23 - MS(ES): m/e 269 (M+H); 25; 26 - MS(ES): m/e 279  
(M+H); 27; 28; 29; 30 - MS(ES): m/e 265 (M+H); 31; 32 - MS(ES):  
30 m/e 255 (M+H); 33; 34; 35; 36; 37 - MS(ES): m/e 242 (M+H); 38; 39  
- MS(ES): m/e 221 (M+H); 40 - MS(ES): m/e 257 (M+H); 41; 42 -  
MS(ES): m/e 250 (M+H); 43 - MS(ES): m/e 277 (M+H); 45 - MS(ES):  
m/e 245 (M+H); 46 - MS(ES): m/e 521 (M+H); 47 - MS(ES): m/e 241  
(M+H); 48 - MS(ES): m/e 314 (M+H); 51 - MS(ES): m/e 360 (M+H); 54  
35 - MS(ES): m/e 340 (M+H); 58; 73 - MS(ES): m/e 367 (M+H); 74 -  
MS(ES): m/e 342 (M+H); 80 - MS(ES): m/e 335 (M+H).

**Example 2**

**(a) Synthesis of key intermediate: 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine**

5



(2-chloro-5-nitro-phenyl)-methanol

To a stirred suspension of sodium borohydride (9.9 mmol) in dry THF (20 ml) at 0°C was added 2-chloro-5-nitrobenzoic acid (4.96 mmol) dissolved in dry THF (5 ml). Boron trifluoride etherate (13.3 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 1 hour. The reaction mixture was quenched with 1N HCl and then partitioned between DCM and water. The organic layer was separated, washed with brine solution, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 0.92g of the desired product; MS(ES): m/e 189 (M+H);  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 8.5 (1H, br s), 8.13 (1H, br dd), 7.54 (1H, d, J 8), 4.89 (2H, s).

2-bromomethyl-1-chloro-4-nitro-benzene

(2-Chloro-5-nitro-phenyl)-methanol (4.9 mmol) was dissolved in DCM (30 ml) and cooled to 0°C. Triphenyl phosphine (5 mmol) was added followed by carbon tetrabromide (4.9 mmol). The reaction mixture was diluted with DCM and washed with water and brine solution. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered and evaporated to yield 1.23g of the desired product; MS (ES): m/e 252 (M+H);  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 8.37 (1H, br s), 8.15

(1H, dd, J 8, 1), 7.61 (1H, d, J 8), 4.63 (2H, s).

3-(2-chloro-5-nitro-benzyloxy)-pyridine

3-Hydroxy pyridine (5.3 mmol) was dissolved in dry DMF (6 ml),  
5 cooled to 0°C and then treated with sodium hydride (60%, 5.5  
mmol). After 20 mins, 2-bromomethyl-1-chloro-4-nitro-benzene 4.9  
mmol) was added in dry DMF (6 ml) and the reaction mixture  
stirred at 0°C for 1 hour. The reaction mixture was quenched  
with water, then partitioned between ethyl acetate and water.  
10 The organic layer was separated, washed with brine solution,  
dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by  
column chromatography on silica. Elution with mixtures of  
petroleum ether and ethyl acetate afforded 0.32g of the desired  
product; MS(ES): m/e 266 (M+H).

15

4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine

3-(2-chloro-5-nitro-benzyloxy)-pyridine (1.2 mmol) was dissolved  
in dioxan:water (5:1, 6 ml), and treated with iron powder (10.9  
mmol) and iron sulfate heptahydrate (2.66 mmol). The reaction  
20 mixture was refluxed for 6 hours, cooled to room temperature and  
filtered. The filtrate was diluted with ethyl acetate and washed  
with saturated bicarbonate and brine solution. The organic layer  
was separated, dried (MgSO<sub>4</sub>), filtered and evaporated to give  
195mg of the desired product; MS(ES): m/e 236 (M+H).

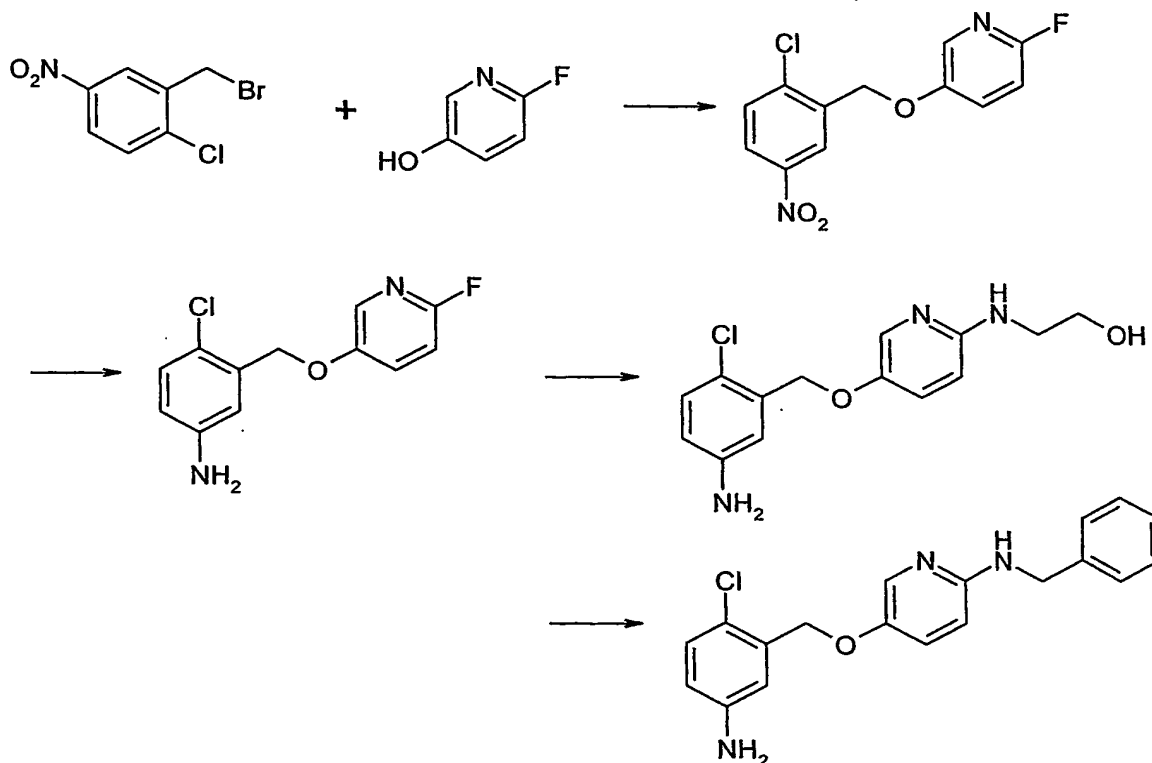
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The corresponding key intermediates 3-(pyridin-3-yloxymethyl)-  
phenylamine, 4-fluoro-3-(pyridin-3-yloxymethyl)-phenylamine and  
4-chloro-3-(6-hydroxymethylamino-pyridin-3-yloxymethyl)-  
phenylamine were synthesised in a similar fashion.

30



(b) Synthesis of key intermediates 4-chloro-3-(6-benzylamino-pyridin-3-yloxymethyl)-phenylamine and 4-chloro-3-(2-amino-pyridin-3-yloxymethyl)-phenylamine



5 5-(2-Chloro-5-nitro-benzyloxy)-2-fluoro-pyridine

To a solution of 2-fluoro-5-hydroxypyridine (1.77 mmol) in DMF (4 ml) was added NaH (60% dispersion in mineral oil, 4.42 mmol) in small portions at room temperature and under an atmosphere of nitrogen. After stirring for 1 hour, tetra-*n*-butylammonium chloride (17.68  $\mu$ mol) was added, followed by 2-chloro-5-nitrobenzyl bromide (5.31 mmol) (see above). After stirring for a further 17 hours, MeOH (2 ml) and then water (2 ml) were added. The DMF was removed *in vacuo* and the residue was partitioned between ethyl acetate (50 ml) and water (25 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The combined organic extracts were then dried ( $\text{MgSO}_4$ ), filtered and concentrated. Purification by flash chromatography eluting with EtOAc/40-60 petroleum ether (1:19) gave the desired compound as a pale yellow oil.  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.23 (2H, s), 6.94 (1H, dd,  $J$  8.8 and 3.5),

7.46-7.51 (1H, m), 7.61 (1H, d,  $J$  8.8), 7.95-7.98 (1H, m), 8.19 (1H, dd,  $J$  8.6 and 2.6), 8.49 (1H, d,  $J$  2.6).

4-Chloro-3-(6-fluoro-pyridin-3-yloxymethyl)-phenylamine

5

To a solution of 5-(2-Chloro-5-nitro-benzyloxy)-2-fluoro-pyridine (5.31 mmol) in dioxane/water (5:1, 30 ml) was added iron powder (47.8 mmol) followed by iron sulphate heptahydrate (11.7 mmol) and the reaction mixture was heated to reflux for a period of 17 hours.

10 Upon cooling, the reaction mixture was filtered through a plug of celite, washed with ethyl acetate (250 ml) and the solvent removed in vacuo. Purification of the residue by flash chromatography eluting with EtOAc/40-60 petroleum ether (3:7) gave the desired compound.  $\delta_H$  (400 MHz;  $d_6$ -DMSO) 5.07 (2H, s), 5.33 (2H, br s), 6.55  
15 (1H, dd,  $J$  8.6 and 2.8), 6.74 (1H, d,  $J$  2.8), 7.09 (1H, d,  $J$  8.6), 7.14 (1H, dd,  $J$  9.1 and 3.0), 7.62-7.68 (1H, m), 7.96 (1H, dd,  $J$  3.0 and 1.8).

2-[5-(5-Amino-2-chloro-benzyloxy)-pyridin-2-ylaminol]-ethanol

20

A stirred solution of 4-chloro-3-(6-fluoro-pyridin-3-yloxymethyl)-phenylamine (0.49 mmol) in ethanolamine (2.5 ml) was heated to 130 °C for 24 hours. Upon cooling, the reaction mixture was partitioned between ethyl acetate (80 ml) and water (40 ml).

The organic layer was separated and the aqueous layer was  
25 extracted with ethyl acetate (2 x 40 ml). The combined organic extracts were then dried ( $MgSO_4$ ), filtered and concentrated in vacuo. Purification by flash chromatography eluting with EtOAc/40-60 petroleum ether (1:1) gave the title compound as a pale yellow oil (85 mg, 56%).  $\delta_H$  (400 MHz;  $CDCl_3$ ) 3.40-3.44 (2H,  
30 m), 3.66 (2H, br s), 3.78 (2H, t,  $J$  4.6), 4.66 (1H, br s), 4.99 (2H, s), 6.42 (1H, d,  $J$  8.8), 6.55 (1H, dd,  $J$  8.6 and 2.8), 6.82 (1H, d,  $J$  2.8), 7.12 (1H, d,  $J$  8.6), 7.15 (1H, dd,  $J$  9.0 and 3.0), 7.80 (1H, d,  $J$  2.8).

35 [5-(5-Amino-2-chloro-benzyloxy)-pyridin-2-yl]-benzylamine

This was prepared in an analogous manner to 2-[5-(5-Amino-2-

chloro-benzyloxy)-pyridin-2-ylamino]-ethanol, but using benzylamine in place of ethanolamine. MS(ES): m/e 340 (M+H).

**Example 2(a):**

**5 Synthesis of compounds where R<sup>4</sup> is phenyl-NH-C(=O) -**

*(a) First method*

Synthesis of N-[4-Chloro-3-pyridin-3-yloxymethyl)-phenyl]-2-morpholin-4-yl-isonicotinamide - 44

10 A stirred solution of 2-morpholin-4-yl-isonicotinic acid (0.24 mmol) in dry DCM (5ml) at 0°C was treated with oxalyl chloride (0.29 mmol) and DMF (one drop). The mixture was stirred at 0°C for 1 hour, then the solvent was removed under reduced pressure.

15 The residue was dissolved in dry DCM (3ml) and treated dropwise with 4-chloro-3-(pyridin-2-yloxymethyl)-phenylamine (0.16mmol) and triethylamine (0.16ml) at 0°C. The reaction mixture was allowed to warm to room temperature overnight, then diluted with DCM and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by  
20 column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 426 (M+H).

25 The following compounds were synthesised using a similar method, but with the appropriate starting materials:

*from 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine*

N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide - 49, MS(ES): m/e 443 (M+H); N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-fluoro-benzamide - 50,  
30 MS(ES): m/e 358 (M+H); N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - 52, MS(ES): m/e 340 (M+H); N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-isonicotinamide - 53, MS(ES): m/e 341 (M+H); N-[3-(2-Amino-pyridin-3-yloxymethyl)-4-chloro-phenyl]-benzamide - 57, MS(ES): m/e 355 (M+H).  
35

from 4-fluoro-3-(pyridin-3-yloxymethyl)-phenylamine

N-[4-Fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - 59,

MS(ES): m/e 323 (M+H); 3-Fluoro-N-[4-fluoro-3-(pyridin-3-

yloxymethyl)-phenyl]-benzamide - 60, MS(ES): m/e 341 (M+H); 3-

- 5 Fluoro-N-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-5-morpholin-4-yl-benzamide - 62, MS(ES): m/e 426 (M+H).

from 3-(pyridin-3-yloxymethyl)-phenylamine

N-[3-(Pyridin-3-yloxymethyl)-phenyl]-benzamide - 66, MS(ES): m/e

- 10 305 (M+H).

(b) Second method

Synthesis of 3-Tert-butyl-N-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - 65

- 15 A stirred solution 4-chloro-3-(pyridin-2-yloxymethyl)-phenylamine (0.14 mmol) in dry DCM (5ml) was treated with EDCI (1.68 mmol) and HOAt (1.68 mmol). 3-Tert-butyl benzoic acid (0.14 mmol) was added and the reaction mixture stirred at room temperature overnight. The reaction mixture was diluted with DCM and washed
- 20 with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES):
- 25 m/e 396 (M+H)

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

- 30 From 4-chloro-3-(6-hydroxymethylamino-pyridin-3-yloxymethyl)-phenylamine

N-{4-Chloro-3-[6-(2-hydroxy-ethylamino)-pyridin-3-yloxymethyl]-phenyl}-3-fluoro-5-morpholin-4-yl-benzamide - 76, MS(ES): m/e 502 (M+H).

35

from 4-chloro-3-(6-benzylamino-pyridin-3-yloxymethyl)-phenylamine  
N-[3-(6-Benzylamino-pyridin-3-yloxymethyl)-4-chloro-phenyl]-3-

fluoro-5-morpholin-4-yl-benzamide - 77, MS(ES): m/e 548 (M+H).

from 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine

- 5 N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-trifluoromethyl-benzamide - 69, MS(ES): m/e 408 (M+H); 3-Chloro-N-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - 70, MS(ES): m/e 374 (M+H).

from 4-fluoro-3-(pyridin-3-yloxymethyl)-phenylamine

- 10 6-Morpholin-4-yl-pyrazine-2-carboxylic acid [4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-amide - 75, MS(ES): m/e 410 (M+H); 1-(2-tert-Butyl-phenyl)-3-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-urea - 78, MS(ES): m/e 394 (M+H).

- 15 from 3-(pyridin-3-yloxymethyl)-phenylamine

3-Fluoro-5-morpholin-4-yl-N-[3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - 67, MS(ES): m/e 408 (M+H).

**Example 2(b):**

- 20 **Synthesis of compounds where R<sup>4</sup> is phenyl-NH-C(=O)-NH-**

Synthesis of 1-(5-tert-Butyl-2H-pyrazol-3-yl)-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea - 71

- A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.21 mmol) in dry DCM (5 ml) at 0°C was treated with  
25 diisopropyl ethylamine (2.13 mmol), followed by triphosgene (0.25 mmol). The mixture was stirred at 0°C for 3 hours, then treated with 3-amino-5-tert-butyl pyrazole (0.42 mmol). The reaction mixture was allowed to warm to room temperature overnight, then solvent was removed under reduced pressure and the residue  
30 partitioned between ethyl acetate and saturated bicarbonate solution. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 20mg of the desired product;  
35 MS(ES): m/e 401 (M+H).

The following compounds were synthesised using a similar method,

but with the appropriate starting materials:

from 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine

1-phenyl-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea - 61,

- 5 MS(ES): m/e 355 (M+H); 1-(5-tert-Butyl-2-phenyl-pyrazol-3-yl)-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea - 64, MS(ES): m/e 477 (M+H); [4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea, 63, MS(ES): m/e 279 (M+H), using 2M aqueous ammonium chloride in place of aromatic amine.

10

from 4-fluoro-3-(pyridin-3-yloxymethyl)-phenylamine

1-[4-Fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-3-(5-isopropyl-[1,3,4]thiadiazol-2-yl)-urea - 81, MS(ES): m/e 388 (M+H).

15 **Example 2(c):**

**Synthesis of compounds where R<sup>4</sup> is phenyl-NH-C(=O)-O-**

Synthesis of [4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-carbamic acid phenyl ester - 79

- 20 A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.21 mmol) and pyridine in dry DCM (0.5 ml) at 0°C was treated with phenyl chloroformate (0.22 mmol). The reaction mixture was warmed to room temperature over 1 hour then diluted with DCM and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated,
- 25 dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 70mg of the desired product; MS(ES): m/e 356 (M+H).

30

**Example 2(d):**

**Synthesis of further compounds where R<sup>4</sup> is phenyl-N**

Synthesis of N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzenesulfonamide - 55 and N-[4-Chloro-3-(pyridin-3-

- 35 yloxymethyl)-phenyl]-bisbenzenesulfonamide - 56

A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-

phenylamine (0.09 mmol) in dry DCM at room temperature was treated with triethylamine (0.18 mmol) and sulfonyl chloride (0.126 mmol). The mixture was stirred at room temperature overnight, then solvent removed under reduced pressure. The residue was diluted with DCM and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of DCM and MeOH afforded the desired products; MS(ES): m/e 376 (M+H) and 516 (M+H).

Synthesis of N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-N'-(3-fluoro-5-morpholin-4-yl-phenyl)-oxalamide - 72

A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.2 mmol) in dry DCM at 0°C was treated with oxalyl chloride (0.2 mmol). The mixture was stirred at room temperature for 1 hour, then treated with aniline (0.4 mmol) and the reaction mixture stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was then diluted with ethyl acetate and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by reverse phase HPLC to afford the desired compound; MS(ES): m/e 383 (M+H).

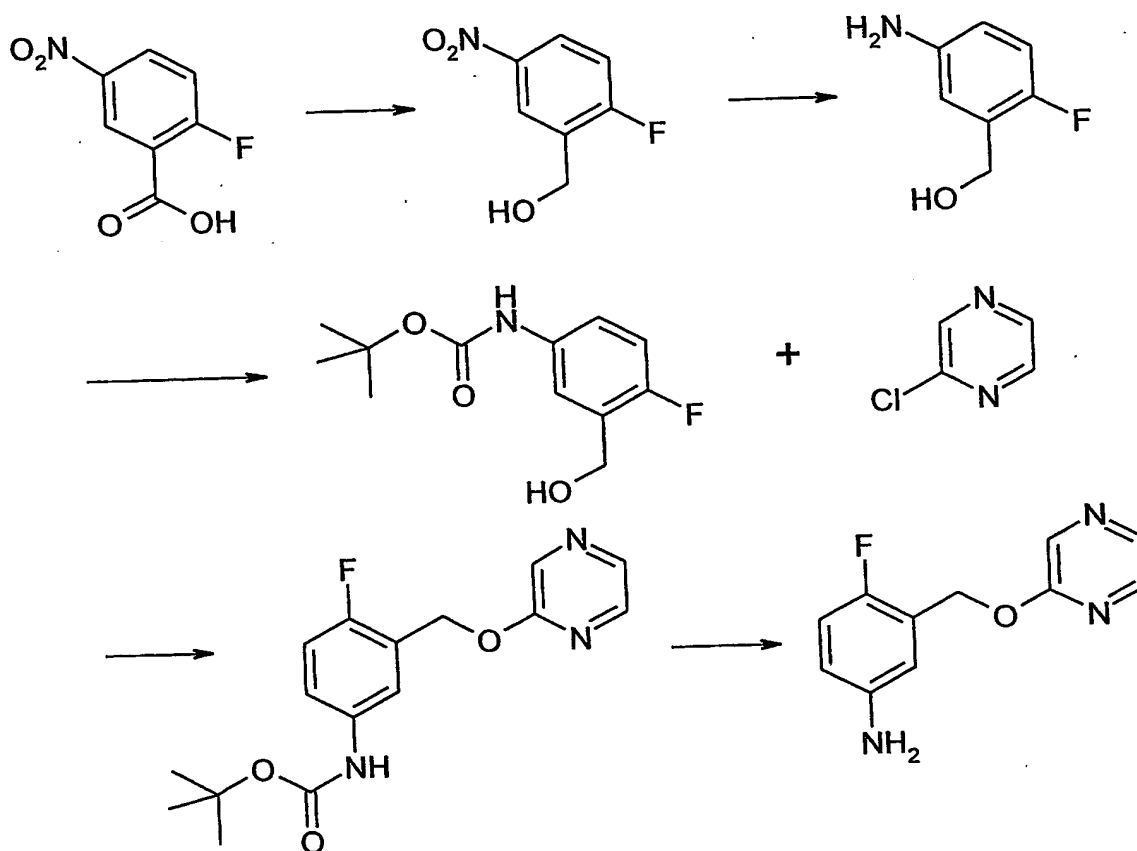
Synthesis of 2-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-isoindole-1,3-dione - 68

A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.21 mmol) in dry chloroform at room temperature was treated with phthalic anhydride (0.21 mmol). The mixture was stirred at room temperature for 1 hour then solvent removed under reduced pressure. The residue was then redissolved in glacial acetic acid and the reaction mixture refluxed overnight. The reaction mixture was then diluted with ethyl acetate and washed with water, saturated bicarbonate solution and brine solution. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered,

evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the title product; MS(ES): m/e 366 (M+H).

5 **Example 3**

(a) **Synthesis of key intermediate: 4-fluoro-3-(pyridin-3-ylloxymethyl)-phenylamine**



10

(2-fluoro-5-nitro-phenyl)-methanol

To a stirred suspension of sodium borohydride (44.5 mmol) in dry THF (80 ml) at 0°C was added 2-fluoro-5-nitrobenzoic acid (2.43 mmol) dissolved in dry THF (50 ml). Boron trifluoride etherate (66.6 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 1 hour. The reaction mixture was quenched with 1N HCl and then partitioned between DCM and water. The organic layer was separated, washed with brine

15



solution, dried ( $\text{MgSO}_4$ ), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 172 ( $\text{M}+\text{H}$ ).

5

(5-Amino-2-fluoro-phenyl)-methanol

(2-fluoro-5-nitro-phenyl)-methanol (0.15 mol) was dissolved in ethanol (100 ml), and treated with 10% Pd/C (15 mmol). The reaction mixture was hydrogenated under an atmosphere of hydrogen gas for 6 hours, then the reaction mixture was filtered through celite. The solvent was evaporated to give the desired compound. MS(ES): m/e 142 ( $\text{M}+\text{H}$ ).

15 (4-Fluoro-3-hydroxymethyl-phenyl)-carbamic acid tert-butyl ester

To a stirred solution of (5-Amino-2-fluoro-phenyl)-methanol (12.4 mmol) in dioxan (40 ml) was added di-(tert-butoxycarbonyloxy)anhydride (BOC anhydride) (13.65 mmol) and sodium carbonate (14.89 mmol) in water (40 ml). The reaction mixture was stirred at room temperature overnight, then partitioned between ethyl acetate and water. The organic layer was separated, washed with brine solution, dried ( $\text{MgSO}_4$ ), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 242 ( $\text{M}+\text{H}$ ).

[4-Fluor-3-(pyrazin-2-yloxymethyl)-phenyl]-carbamic acid tert-butyl ester

30 To a stirred solution of (4-Fluoro-3-hydroxymethyl-phenyl)-carbamic acid tert-butyl ester (12.4 mmol) in dry DMF (50 ml) was added sodium hydride (60% dispersion in mineral oil, 25.7 mmol) and the reaction mixture stirred for 30 minutes at room temperature. 2-Chloropyrazine (11.37 mmol) was added and the reaction mixture stirred at room temperature overnight. The reaction mixture was quenched with water and then partitioned between ethyl and water. The organic layer was separated, washed

with brine solution, dried ( $\text{MgSO}_4$ ), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 320 (M+H).

5

4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine

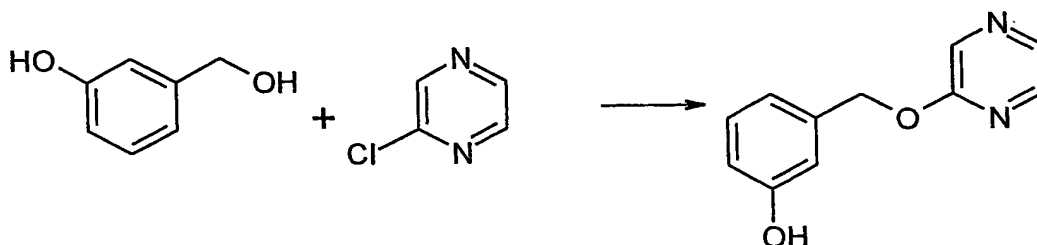
[4-Fluor-3-(pyrazin-2-yloxymethyl)-phenyl]-carbamic acid tert-butyl ester (9.4 mmol) was treated with saturated ethyl acetate/HCl solution (100ml) at room temperature for 1 hour. The precipitated product was filtered, washed with diethyl ether and dried to afford the desired product. MS(ES): m/e 220 (M+H).

10

The corresponding key intermediate 4-chloro-3-(pyrazin-2-yloxymethyl)-phenylamine was synthesised in a similar fashion.

15

(b) Synthesis of key intermediate: 3-(pyrazin-2-yloxymethyl)-phenol



20

3-Hydroxybenzyl alcohol (8.1 mmol) was dissolved in dry DMF (10 ml), treated with sodium hydride (60% suspension in mineral oil, 9 mmol) and stirred at 0°C for 30 minutes. 2-Chloropyrazine (8.1 mmol) was added and the reaction mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 1M HCl. The organic layer was separated, washed with saturated sodium bicarbonate solution and brine solution respectively, then dried ( $\text{MgSO}_4$ ), filtered and evaporated to afford the desired product. MS(ES): m/e 203 (M+H).

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30

Example 3(a):

Synthesis of compounds where  $\text{R}^4$  is phenyl-NH-C(=O)-

Synthesis of N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-phenoxy-benzamide - 102

A stirred solution of 4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine (0.46 mmol) in dry DMF (4ml) was treated with EDCI (0.55 mmol) and HOBt (0.55 mmol). 3-Phenoxy benzoic acid (0.59 mmol) was added and the reaction mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed with saturated bicarbonate solution and brine solution, then the organic layer was separated, dried (MgSO<sub>4</sub>), filtered and evaporated. The residue was purified by column chromatography on silica, eluting with mixtures of petroleum ether and ethyl acetate to afford the desired product. MS(ES): m/e 416 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

*from 4-fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine*

N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(morpholine-4-sulfonyl)-benzamide - 98; 4-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide - 101, MS(ES): m/e 380 (M+H); 3-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide - 103, MS(ES): m/e 380 (M+H);

6-(3H-Benzotriazol-1-yloxy)-2-chloro-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - 104, MS(ES): m/e 494 (M+H);

2-Chloro-6-methoxy-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - 105, MS(ES): m/e 391 (M+H);

3-Methyl-5-phenyl-isoxazole-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - 122, MS(ES): m/e 405 (M+H);

5-(2-Methyl-thiazol-4-yl)-isoxazole-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - 124, MS(ES): m/e 412 (M+H);

5-Phenyl-[1,3,4]oxadiazole-2-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - 126, MS(ES): m/e 392

- (M+H);  
Naphthalene-2-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **131**, MS(ES): m/e 374 (M+H);  
Biphenyl-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **133**, MS(ES): m/e 400 (M+H);  
5 2-Benzyl-5-tert-butyl-2H-pyrazole-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **135**, MS(ES): m/e 460 (M+H);  
5-tert-Butyl-2-(4-fluoro-benzyl)-2H-pyrazole-3-carboxylic acid  
10 [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **136**, MS(ES): m/e 478 (M+H);  
6-Methyl-imidazo[2,1-b]thiazole-5-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **144**, MS(ES): m/e 384 (M+H);  
15 3,5-Di-tert-butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide - **146**, MS(ES): m/e 436 (M+H);  
1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **147**, MS(ES): m/e 431 (M+H);  
20 2,6-Di-morpholin-4-yl-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **150**, MS(ES): m/e 496 (M+H);  
N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(2-methyl-thiazol-4-yl)-benzamide - **151**, MS(ES): m/e 421 (M+H).  
25  
from 4-chloro-3-(pyrazin-2-yloxymethyl)-phenylamine  
N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide - **92**, MS(ES): m/e 278 (M+H);  
N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-2-morpholin-4-yl-  
30 isonicotinamide - **93**, MS(ES): m/e 427 (M+H);  
N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide, **94**, MS(ES): m/e 444 (M+H).

35 **Example 3(b):**

**Synthesis of compounds where R<sup>4</sup> is phenyl-NH-C(=O)-NH-**

Synthesis of 1-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - 106

A stirred solution of 4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine (0.39 mmol) in dry DCM (10 ml) at 0°C was treated with diisopropyl ethylamine (3.9 mmol), followed by triphosgene (0.46 mmol). The mixture was stirred at 0°C for 3 hours, then treated with 5-tert-butyl-2-phenyl-2H-pyrazol-3-ylamine (0.45 mmol). The reaction mixture was allowed to warm to room temperature overnight, then solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and saturated bicarbonate solution. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 20mg of the desired product. MS(ES): m/e 461 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

*from 4-fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine*

- 1-(5-Cyclopropylmethyl-[1,3,4]thiadiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **96**, MS(ES): m/e 401 (M+H);  
1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-isopropyl-[1,3,4]thiadiazol-2-yl)-urea - **97**, MS(ES): m/e 389 (M+H);  
1-(4-tert-Butyl-thiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **100**, MS(ES): m/e 402 (M+H);  
1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-phenyl-[1,3,4]thiadiazol-2-yl)-urea - **115**, MS(ES): m/e 423 (M+H);  
1-(4,6-Dimethyl-benzothiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **116**, MS(ES): m/e 424 (M+H);  
1-[5-(4-Chloro-phenyl)-thiazol-2-yl]-3-[4-fluoro-3-(pyrazin-2-loxymethyl)-phenyl]-urea - **117**, MS(ES): m/e 457 (M+H);  
1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-phenyl-1H-pyrazol-3-yl)-urea - **118**, MS(ES): m/e 405 (M+H);  
1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-phenyl-1H-pyrazol-3-yl)-urea - **119**, MS(ES): m/e 405 (M+H);  
1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-[5-(tetrahydro-furan-2-yl)-[1,3,4]thiadiazol-2-yl]-urea - **120**, MS(ES): m/e 417

- (M+H);  
1-(5-Benzyl-[1,3,4]thiadiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **121**, MS(ES): m/e 437 (M+H);  
1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-phenyl-  
5 thiazol-2-yl)-urea - **123**, MS(ES): m/e 422 (M+H);  
1-[5-tert-Butyl-2-(2,4-difluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **125**, MS(ES): m/e 497 (M+H);  
1-[5-tert-Butyl-2-(4-chloro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-  
10 3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **127**, MS(ES): m/e 496 (M+H);  
1-[5-(4-Chloro-phenyl)-2-phenyl-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **128**, MS(ES): m/e 516 (M+H);  
15 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **130**, MS(ES): m/e 475 (M+H);  
1-[5-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **132**, MS(ES): m/e 534 (M+H);  
20 1-(2,5-Diphenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **134**, MS(ES): m/e 481 (M+H);  
1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-[5-(tetrahydrofuran-2-yl)-[1,3,4]thiadiazol-2-yl]-urea - **140**, MS(ES): m/e 434 (M+H);  
25 (M+H);  
1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-methylsulfanyl-[1,3,4]thiadiazol-2-yl)-urea - **149**, MS(ES): m/e 393 (M+H);  
1-(2-Benzyl-5-tert-butyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-  
30 2-yloxymethyl)-phenyl]-urea - **153**, MS(ES): m/e 475 (M+H);  
1-(2-Benzothiazol-2-yl-5-tert-butyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **155**, MS(ES): m/e 519 (M+H);  
1-[5-tert-Butyl-2-(6-chloro-pyridazin-3-yl)-2H-pyrazol-3-yl]-3-  
35 [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **156**, MS(ES): m/e 498 (M+H);

- 1-[5-tert-Butyl-2-(2,6-dimethyl-pyrimidin-4-yl)-2H-pyrazol-3-yl]-  
3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **157**, MS(ES):  
m/e 491 (M+H);
- 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-  
5 methanesulfinyl-[1,3,4]thiadiazol-2-yl)-urea - **159**, MS(ES): m/e  
409 (M+H);
- 1-(5-tert-Butyl-2-pyridin-4-yl-2H-pyrazol-3-yl)-3-[4-fluoro-3-  
(pyrazin-2-yloxymethyl)-phenyl]-urea - **160**, MS(ES): m/e 462  
(M+H);
- 10 1-[2-(4-Fluoro-phenyl)-5-(tetrahydro-furan-2-yl)-2H-pyrazol-3-  
yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **161**,  
MS(ES): m/e 493 (M+H);
- 1-[5-tert-Butyl-2-(4-methanesulfonyl-phenyl)-2H-pyrazol-3-yl]-3-  
[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **163**, MS(ES):  
15 m/e 540 (M+H);
- 1-[2-(4-tert-Butyl-phenyl)-5-cyclopropyl-2H-pyrazol-3-yl]-3-[4-  
fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **164**, MS(ES): m/e  
501 (M+H);
- 1-[2-(4-Fluoro-phenyl)-5-(tetrahydro-pyran-4-yl)-2H-pyrazol-3-  
20 yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **165**,  
MS(ES): m/e 507 (M+H).

**Example 3(c):**

**Synthesis of compounds where R<sup>4</sup> is phenyl-NH-C(=O)-O-**

- 25 Synthesis of [4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-carbamic  
acid 3-trifluoromethyl-phenyl ester - 99

A stirred solution of 4-Fluoro-3-(pyrazin-2-yloxymethyl)-  
phenylamine (0.21 mmol) and pyridine (0.025ml) in DCM (1 ml) at  
0°C was treated with 3-trifluoromethyl phenyl chloroformate (0.22  
30 mmol) in DCM (0.2 ml). The mixture was warmed to room  
temperature over 1 hour, then diluted with DCM, washed with 5%  
citric acid solution, saturated sodium hydrogen carbonate  
solution and brine solution. Dried (MgSO<sub>4</sub>), filtered, evaporated  
and the residue purified by column chromatography on silica,  
35 eluting with mixtures of petroleum ether and ethyl acetate to  
afford the desired product. MS(ES): m/e 408 (M+H).

**Example 3(d):**

**Synthesis of compounds where  $R^4$  is phenyl-O-C(=O)-NH-**

**Synthesis of Phenyl-carbamic acid 3-(pyrazin-2-yloxymethyl)-**

5 **phenyl ester - 107**

A stirred solution 3-(pyrazin-2-yloxymethyl)-phenol (0.49 mmol) in diethyl ether (10 ml) at room temperature was treated with phenylisocyanate (0.49 mmol) and triethylamine (4 drops). The mixture was stirred at room temperature overnight, then the solid precipitate was filtered off, washed with cold ether and dried. The solid was purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 322 (M+H).

15

**Example 3(e):**

**Synthesis of compounds where  $R^4$  is dichlorophenyl and  $R^1$  is C(=O)N**

**Synthesis of 5-(2,6-dichloro-benzyloxy)-pyrazine-2-carboxylic acid (2-sulfamoyl-ethyl)-amide - 138**

20 A stirred solution of 5-(2,6-dichloro-benzyloxy)-pyrazine-2-carboxylic acid (0.37 mmol) in dry DMF (5 ml) at room temperature was treated with triethylamine (0.9 mmol), EDCI (0.45 mmol) and HOBt (0.45 mmol). The mixture was stirred at room temperature for 30 mins, then treated with 2-amino-ethanesulfonic acid amide HCl salt (0.45 mmol). The reaction mixture was allowed to warm to room temperature overnight, then solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was separated, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 406 (M+H).

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The starting material 5-(2,6-dichloro-benzyloxy)-pyrazine-2-carboxylic acid was prepared as follows:

35 (i) Lithium-5-chloro-pyrazine-2-carboxylate

5-Chloro-pyrazine-2-carboxylic acid methyl ester (2.9 mmol) was dissolved in tetrahydrofuran/water (5:1, 10ml), treated with



lithium hydroxide (3.04 mmol) and stirred at room temperature overnight. The solvent was removed under reduced pressure to give the desired compound.  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 8.5 (1H, br s), 8.13 (1H, br dd), 7.54 (1H, d, J 8), 4.89 (2H, s).

- 5 (ii) 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid 2,6-Dichlorobenzyl alcohol (1.1 mmol) was dissolved in dry DMF (5 ml) and treated with sodium hydride (60% dispersion in mineral oil, 1.21 mmol). The mixture was stirred at room temperature for 30 mins, then treated with lithium-5-chloro-pyrazine-2-
- 10 carboxylate (1 mmol) and stirred at reflux overnight. The reaction mixture was partitioned between ethyl acetate and water, then the organic layer was separated, dried (MgSO<sub>4</sub>), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and diethyl
- 15 ether afforded the title product. MS(ES): m/e 300 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

- 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid ethylamide
- 20 - 111;
- 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (2-hydroxy-ethyl)-amide - 112;
- 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide - 113;
- 25 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-amide - 137;
- 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (1,1-dimethyl-2-pyridin-4-yl-ethyl)-amide - 139.

30 **Example 3(f):**

**Synthesis of compounds where R<sup>4</sup> is dichlorophenyl and R<sup>1</sup> is NH**  
**Synthesis of 2-[5-(2,6-Dichloro-benzyloxy)-pyrazin-2-ylamino]-**  
**ethanol - 158**

- A stirred solution of [5-(2,6-dichloro-benzyloxy)-pyrazin-2-
- 35 yl]carbamic acid tert-butyl ester (0.27 mmol) in dry DMF (5 ml) at room temperature was treated with sodium hydride (60%

dispersion in mineral oil, 0.35 mmol). The mixture was stirred at room temperature for 30 mins, treated with (2-bromo-ethoxy)-trimethyl-silane (0.32 mmol) and allowed to reflux overnight. The reaction mixture was partitioned between ethyl acetate and water, the organic layer separated, dried (MgSO<sub>4</sub>), filtered and evaporated to dryness. The residue was then taken up in dry DCM (5 ml), treated with TFA (0.5 ml) and stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the title product. MS(ES): m/e 315 (M+H).

The starting material [5-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]carbamic acid tert-butyl ester was prepared as follows:

- (i) 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carbonyl azide  
5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (14 mmol) was dissolved in thionyl chloride (30 ml) and heated at reflux for 2 hours. The thionyl chloride was removed under reduced pressure with toluene, the residue dissolved in acetone (60 ml), treated with sodium azide (16.9 mmol) and then stirred overnight at room temperature. The reaction mixture was diluted with water and the solvent removed under reduced pressure. The residue was partitioned between DCM and water then the organic layer was separated, dried (MgSO<sub>4</sub>), filtered and evaporated to afford the title product. MS(ES): m/e 325 (M+H)
- (ii) [5-(2,6-Dichloro-benzyloxy)-pyrazin-2-yl]carbamic acid tert-butyl ester  
5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carbonyl azide (0.31 mmol) was dissolved in toluene (2 ml) and treated with t-butanol (0.6 mmol). The mixture was heated to 100°C in a sealed tube for 15 mins, then solvent removed under reduced pressure. The residue was purified by column chromatography on silica, eluting with mixtures of petroleum ether and ethyl acetate to give the title product. MS(ES): m/e 371 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

Benzyl-[5-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-amine - 141;

[5-(2,6-Dichloro-benzyloxy)-pyrazin-2-yl]-methyl-amine - 148;  
4-[5-(2,6-Dichloro-benzyloxy)-pyrazin-2-yl]-morpholine -  
152;  
[5-(2,6-Dichloro-benzyloxy)-pyrazin-2-yl]-(1-phenyl-ethyl) -amine  
5 - 154.

The following compounds were made by analogous methods to those described above:

10 82 - MS(ES): m/e 252 (M+H); 83 - MS(ES): m/e 330 (M+H); 84; 85 -  
MS(ES): m/e 236 (M+H); 86 - MS(ES): m/e 202 (M+H); 87 - MS(ES):  
m/e 255 (M+H); 88; 89 - MS(ES): m/e 336 (M+H); 90 - MS(ES): m/e  
270 (M+H); 91 - MS(ES): m/e 236 (M+H); 95 - MS(ES): m/e 401  
(M+H); 108 - MS(ES): m/e 311 (M+H); 109 - MS(ES): m/e 337 (M+H);  
15 110 - MS(ES): m/e 270 (M+H); 114 - MS(ES): m/e 369 (M+H); 129 -  
MS(ES): m/e 461 (M+H); 142 - MS(ES): m/e 444 (M+H); 143 - MS(ES):  
m/e 433 (M+H); 145; 162 - MS(ES): m/e 409 (M+H); 166 - MS(ES):  
m/e 354 (M+H).

20 p38 MAP kinase assay

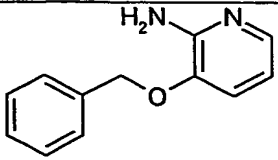
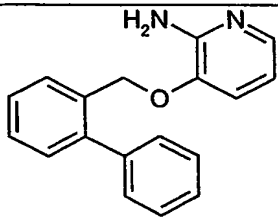
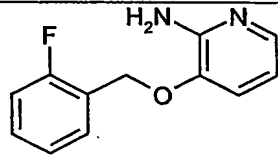
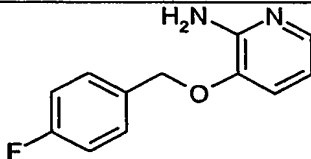
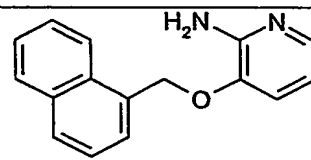
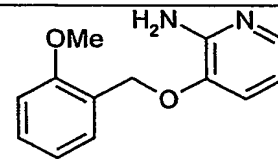
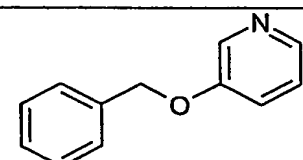
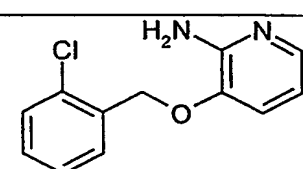
In 1 ml of fresh assay buffer (25 mM HEPES pH 7.4, 25 mM  $\beta$ -  
glycerphosphate, 5 mM EDTA, 15 mM  $MgCl_2$ , 100  $\mu$ M ATP, 1 mM sodium  
orthovanadate, 1 mM DTT), 35  $\mu$ g of inactive purified p38 and 0.12  
25  $\mu$ g of active MKK6 (1688 U/mg - Upstate Biotechnology) are mixed  
and incubated at room temperature overnight to activate the p38.

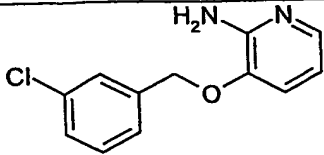
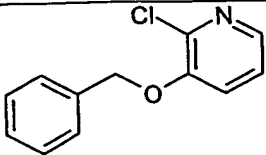
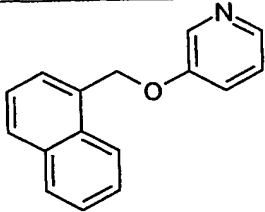
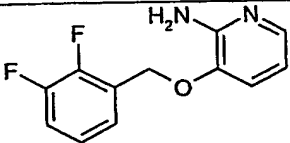
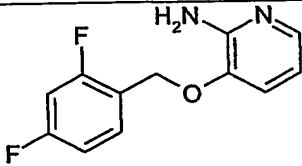
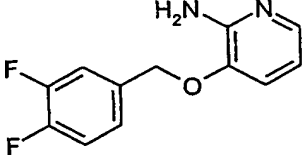
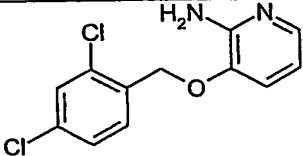
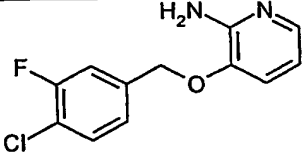
The activated p38 is then diluted 1:6 with assay buffer, and 20  
 $\mu$ l mixed with 25  $\mu$ l of MBP mix (300  $\mu$ l 10 x strength assay  
buffer, 300  $\mu$ l of 10 mM DTT & 10 mM sodium orthovanadate, 1.7 ml  
30  $H_2O$ , 50  $\mu$ Ci  $\gamma^{33}P$ -ATP, 200  $\mu$ l of myelin basic protein (MBP) (5  
mg/ml)) and added to 96 well plates along with 5  $\mu$ l of various  
dilutions of the test compound in DMSO (up to 10%). The reaction  
is allowed to proceed for 50 minutes before being stopped with an  
excess of ortho-phosphoric acid (30  $\mu$ l at 2%).

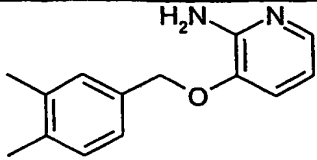
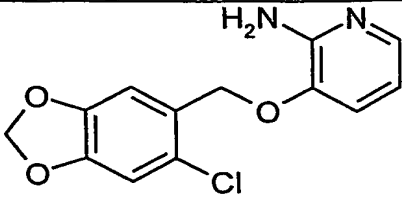
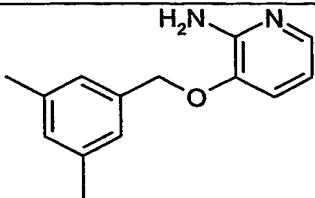
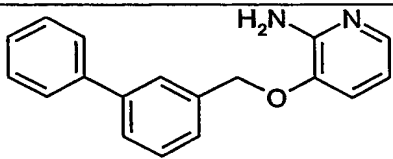
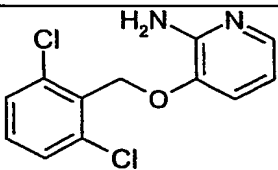
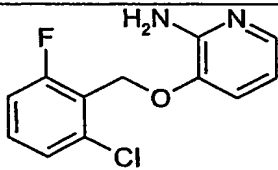
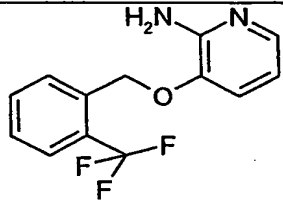
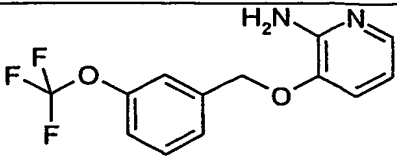
$\gamma$ -<sup>33</sup>P-ATP which remains unincorporated into the myelin basic protein is separated from phosphorylated MBP on a Millipore MAPH filter plate. The wells of the MAPH plate are wetted with 0.5% orthophosphoric acid, and then the results of the reaction are  
5 filtered with a Millipore vacuum filtration unit through the wells. Following filtration, the residue is washed twice with 200  $\mu$ l of 0.5% orthophosphoric acid. Once the filters have dried, 25  $\mu$ l of Microscint 20 scintillant is added, and then counted on  
10 a Packard Topcount for 30 seconds.

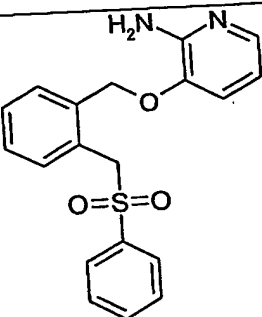
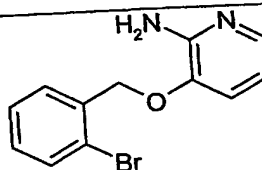
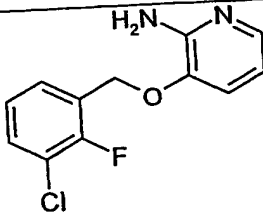
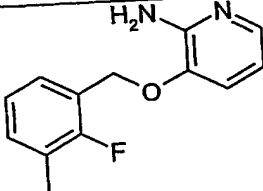
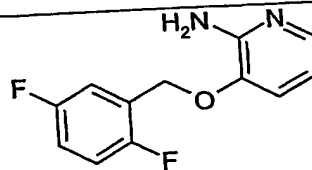
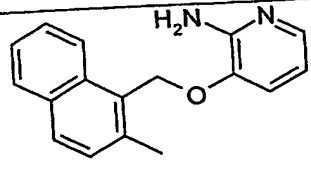
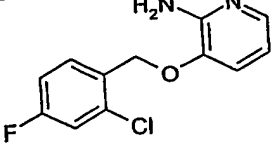
The % inhibition of the p38 activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the p38 activity ( $IC_{50}$ ).

Table 1

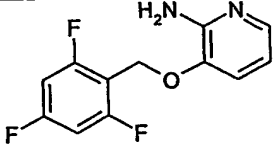
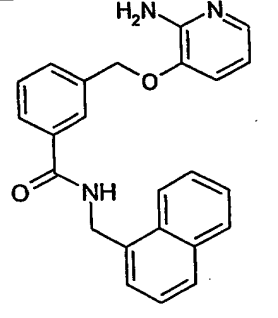
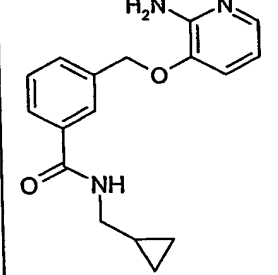
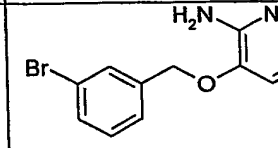
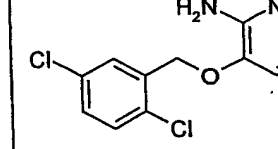
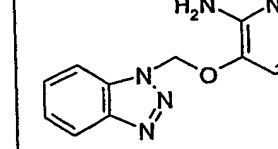
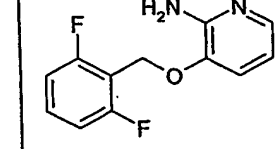
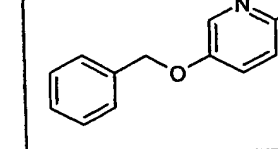
Compound	Structure	IC <sub>50</sub> (μM)
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3		<1000
4		<2000
5		<200
6		<1000
7		<2000
8		<1000

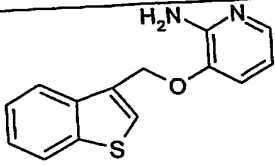
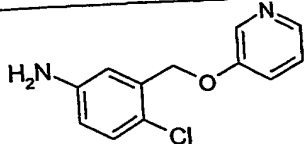
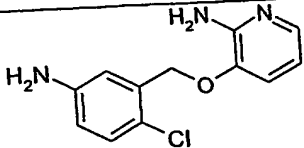
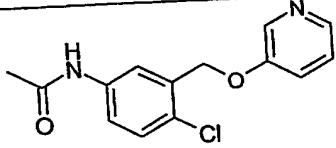
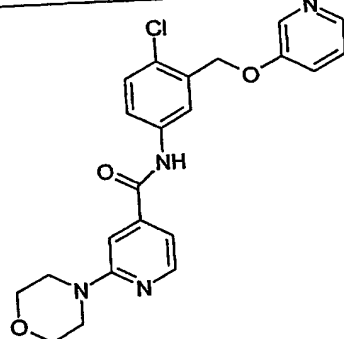
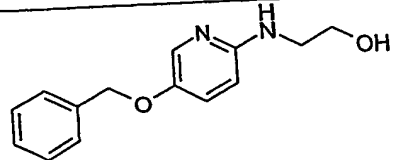
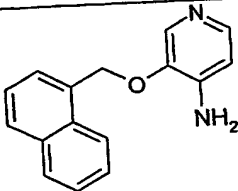
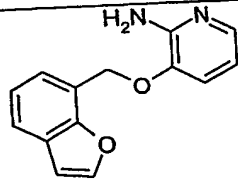
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15		<1000
16		<200

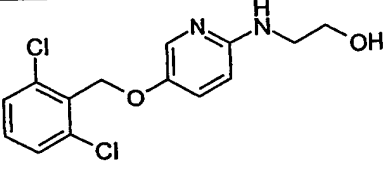
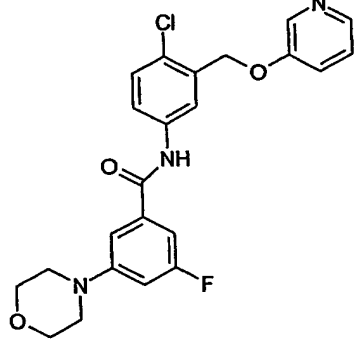
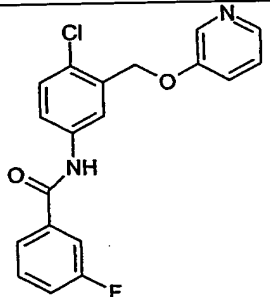
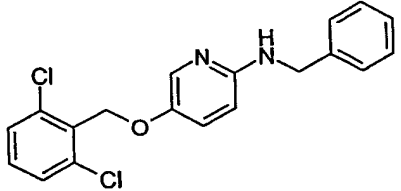
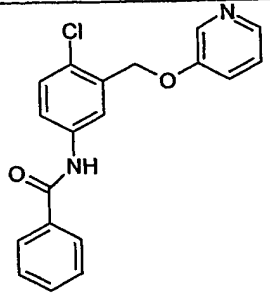
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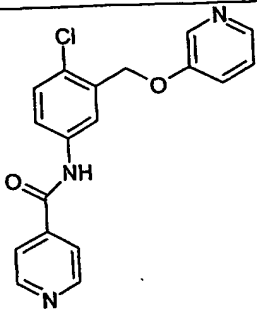
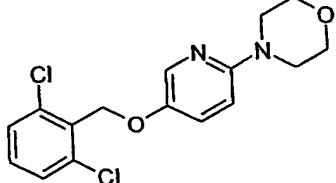
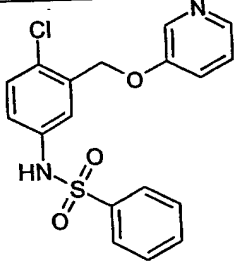
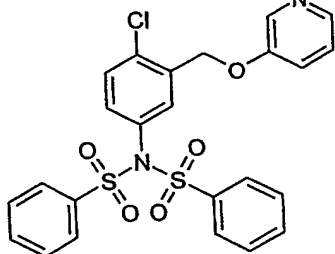
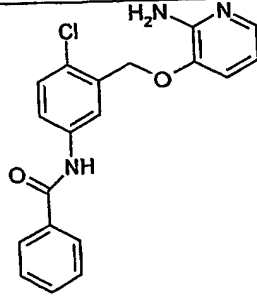
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31		<1000

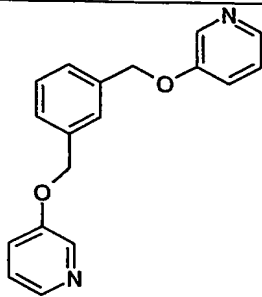
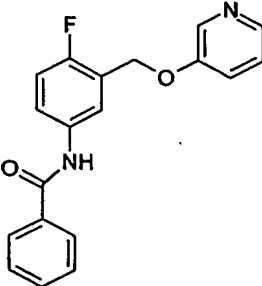
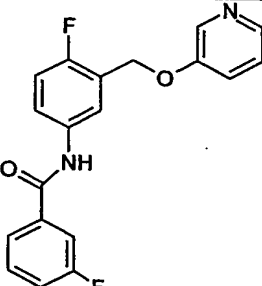
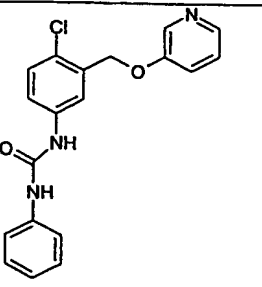
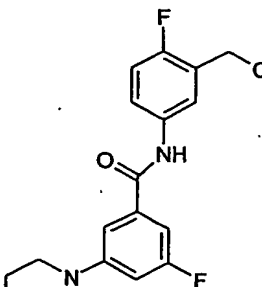


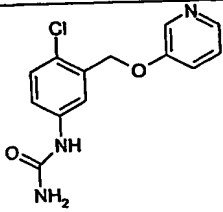
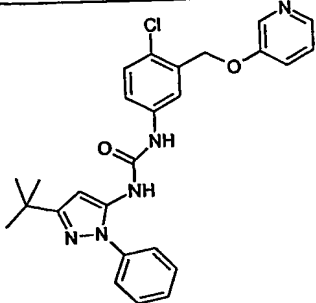
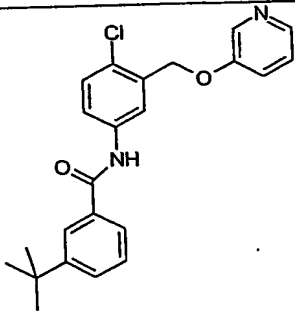
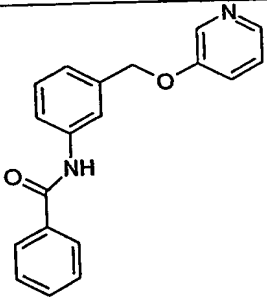
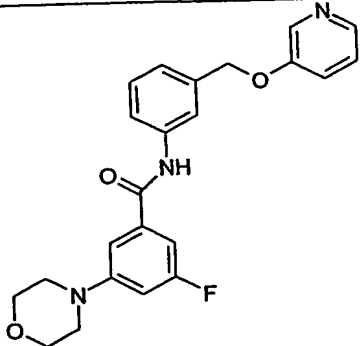
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39		<1000

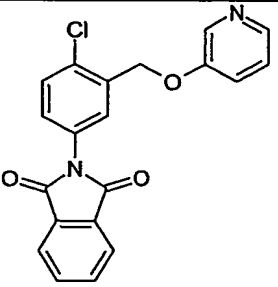
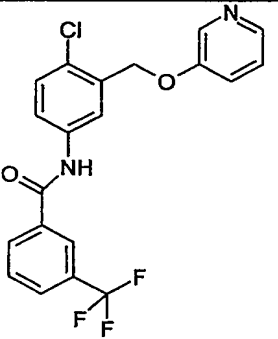
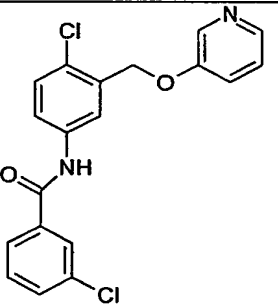
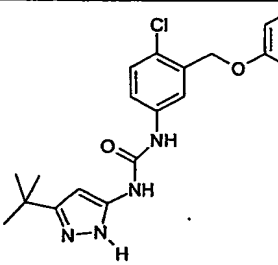
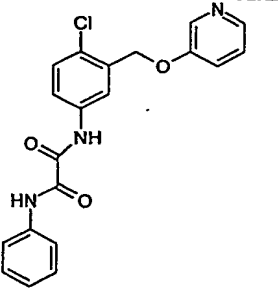
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45		<200
46		<1000
47		<1000

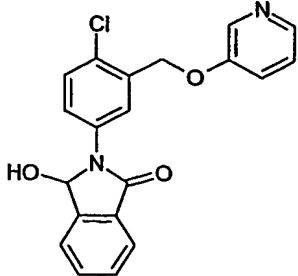
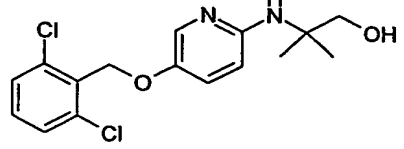
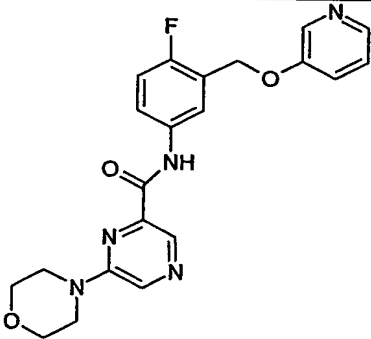
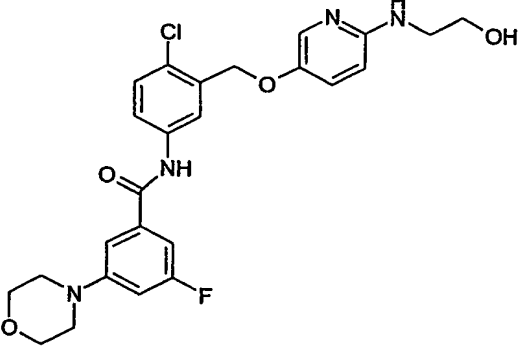
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49		<2
50		<200
51		<200
52		<20

53	 <chem>Nc1cccnc1C(=O)Nc2ccc(Cl)cc2COc3ccncc3</chem>	<200
54	 <chem>Nc1cccnc1C(=O)Nc2ccc(Cl)c(Cl)c2COc3ccncc3N4CCOCC4</chem>	<1000
55	 <chem>NS(=O)(=O)c1ccc(Cl)cc1COc2ccncc2</chem>	<200
56	 <chem>c1ccc(cc1)S(=O)(=O)N(c2ccc(Cl)cc2COc3ccncc3)S(=O)(=O)c4ccccc4</chem>	<1000
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62		<2

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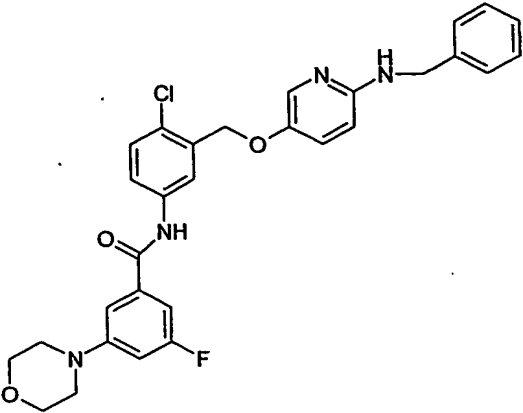
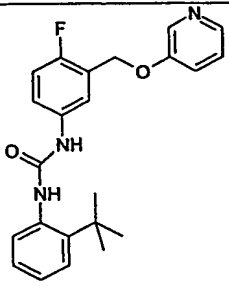
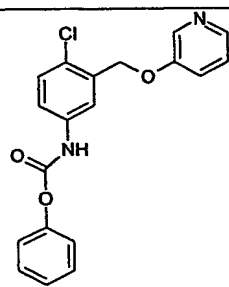
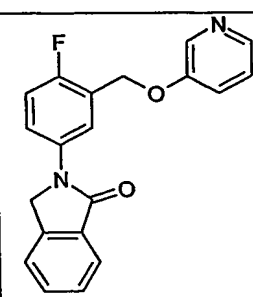
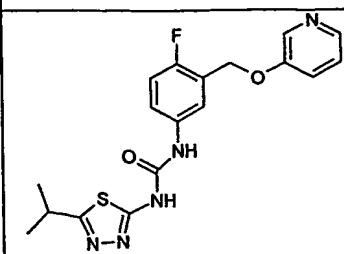
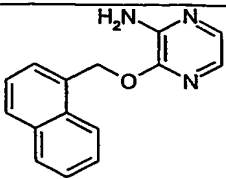
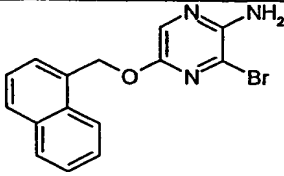
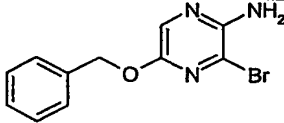
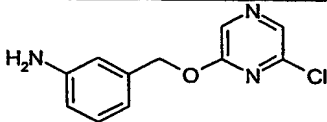
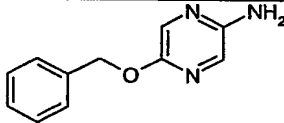
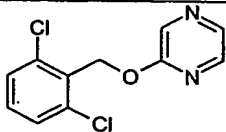
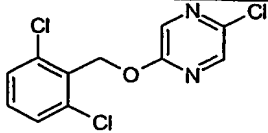
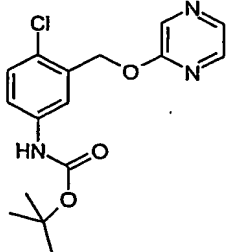
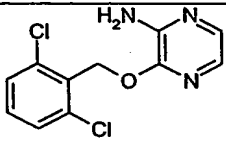
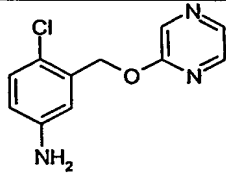
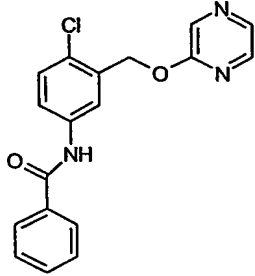
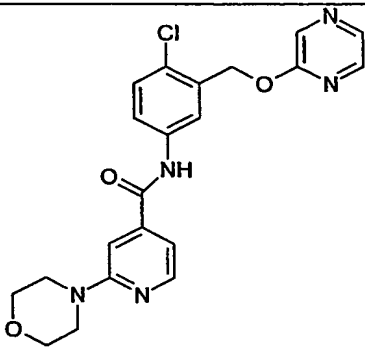
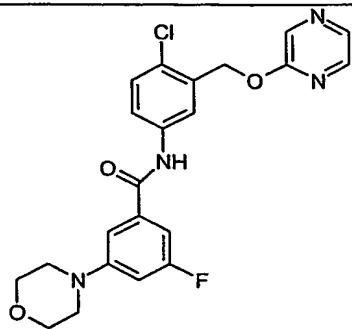
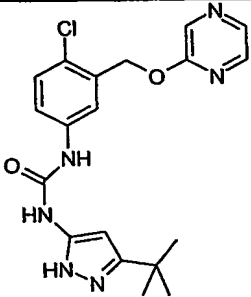
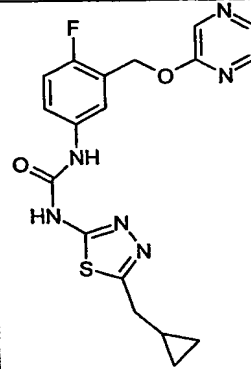
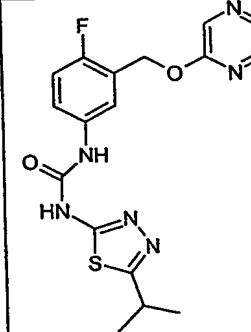
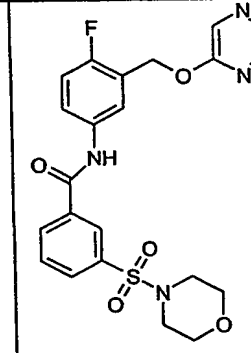
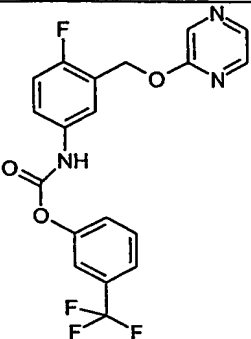
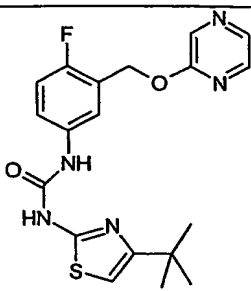
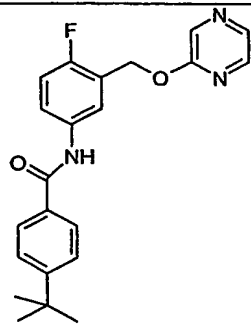
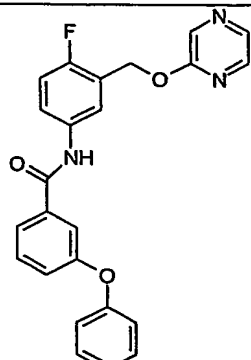
77		<2
78		<20
79		<20
80		<1000
81		<20

Table 2

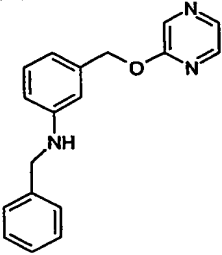
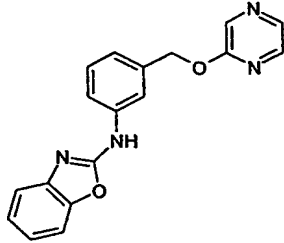
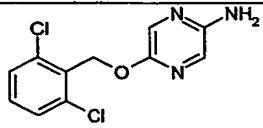
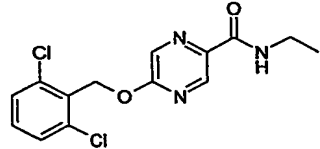
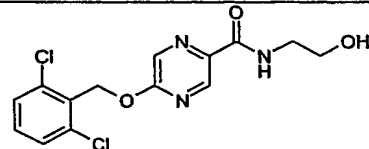
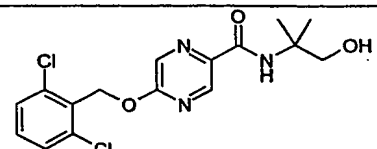
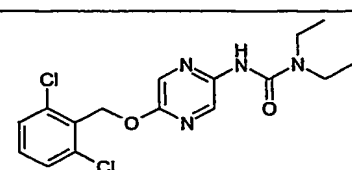
Compound	Structure	IC <sub>50</sub> (μM)
82		<1000
83		<1000
84		<1000
85		<1000
86		<1000
87		<200
88		<1000
89		<1000

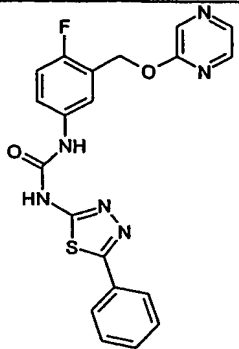
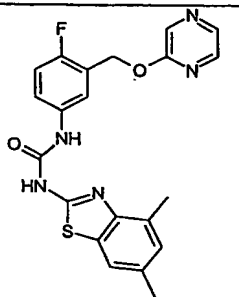
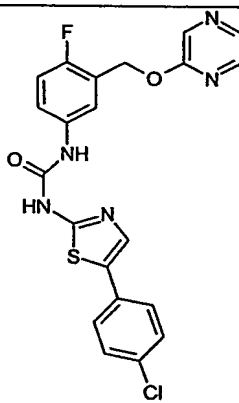
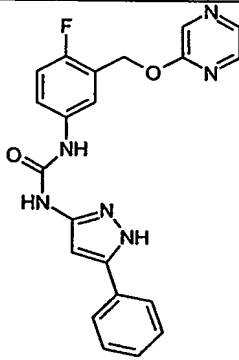
90	 <chem>NC1=NC=CC(OCc2cc(Cl)c(Cl)cc2)=N1</chem>	<1000
91	 <chem>Nc1ccc(OCc2ccncc2)cc1</chem>	<1000
92	 <chem>O=C(NCc1ccccc1)c2ccc(OCc3ccncc3)cc2</chem>	<20
93	 <chem>Clc1ccc(COC2=CN=CN=C2)cc1NC(=O)c3cc4ncc(N5CCOCC5)cc4cc3</chem>	<2
94	 <chem>Fc1cc(NC(=O)c2cc3ncc(N4CCOCC4)cc3cc2)cc(Cl)c1COC5=CN=CN=C5</chem>	<2

95		<20
96		<2
97		<20
98		<2

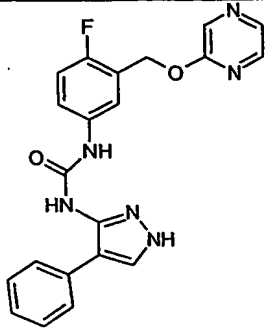
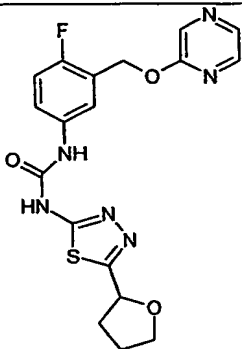
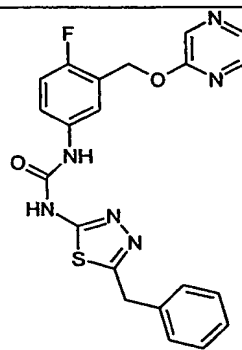
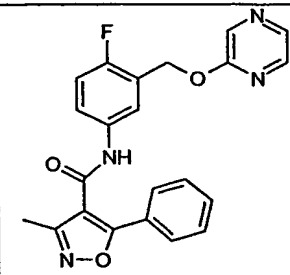
99	 <chem>Fc1ccc(cc1)C(=O)Nc2ccc(cc2)C(F)(F)F</chem>	<20
100	 <chem>CC(C)(C)c1nc(s1)NC(=O)Nc2ccc(cc2)C(F)cc3ccncc3</chem>	<20
101	 <chem>CC(C)(C)c1ccc(cc1)C(=O)Nc2ccc(cc2)C(F)cc3ccncc3</chem>	<20
102	 <chem>c1ccc(cc1)Oc2ccccc2C(=O)Nc3ccc(cc3)C(F)cc4ccncc4</chem>	<2

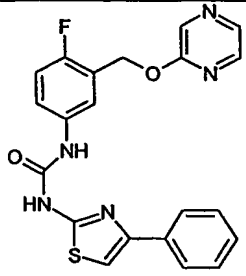
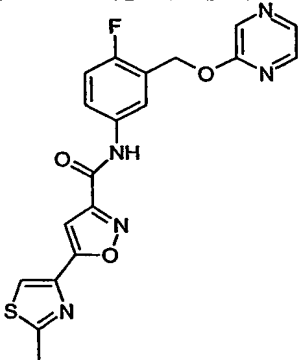
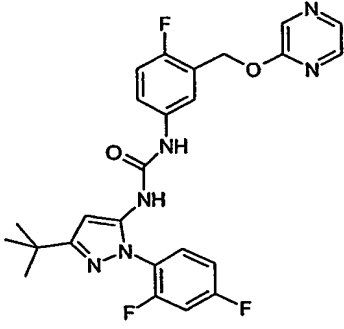
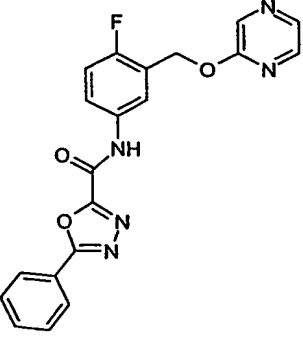


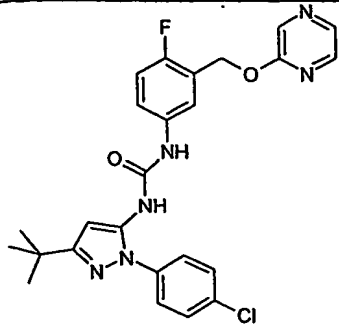
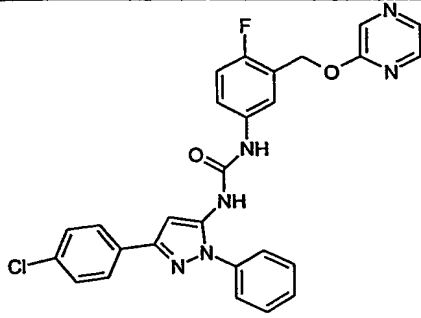
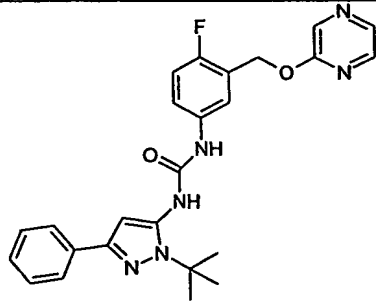
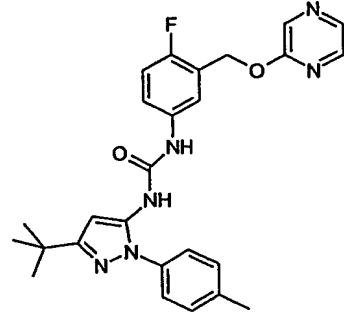
108		<1000
109		<200
110		<200
111		<1000
112		<1000
113		<20
114		<200

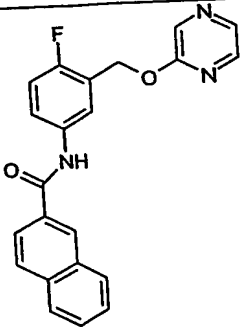
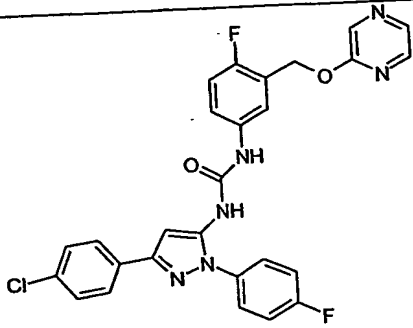
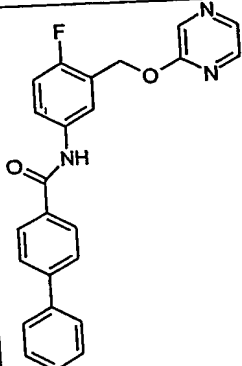
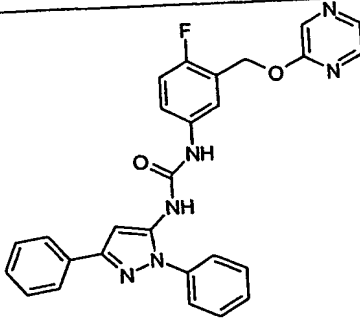
115		<200
116		<1000
117		<200
118		<2

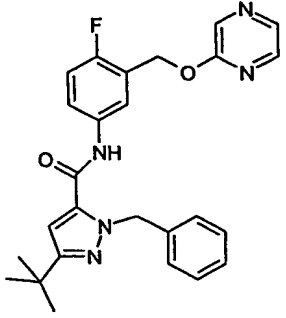
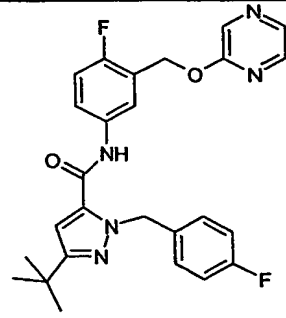
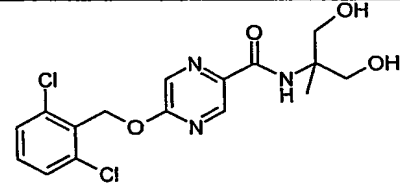
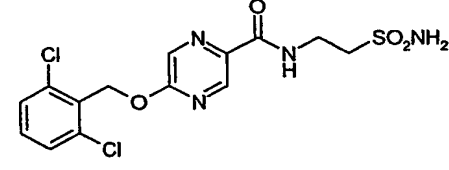
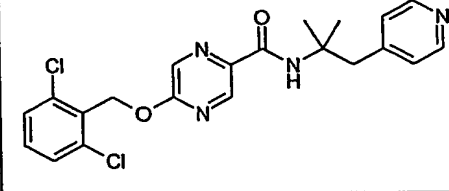
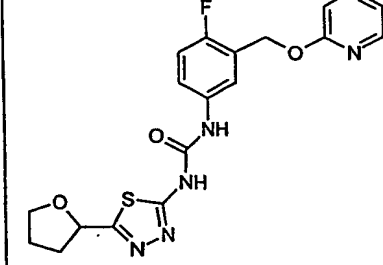


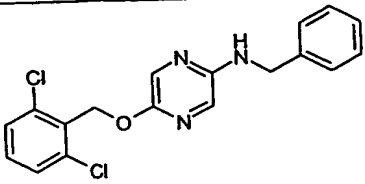
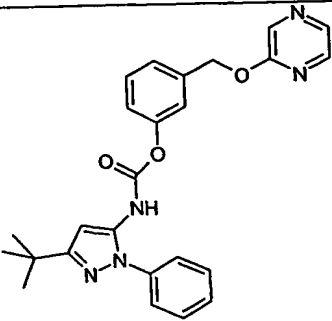
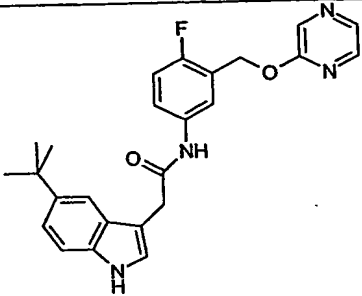
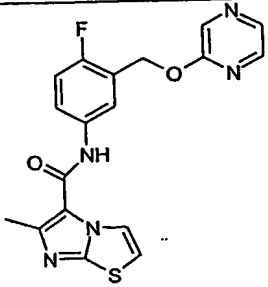
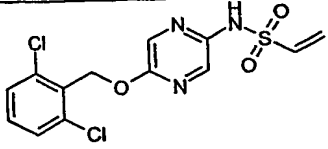
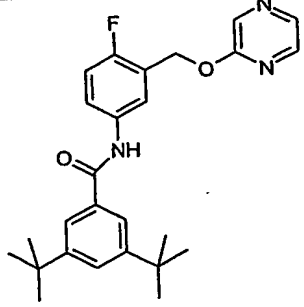
119		<20
120		<2
121		<2
122		<200

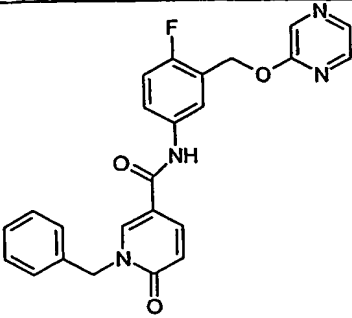
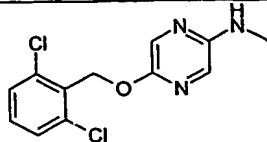
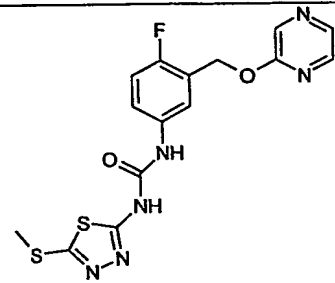
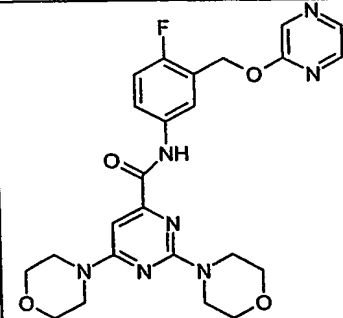
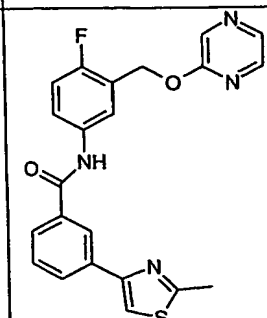
123		<20
124		<200
125		<2
126		<2

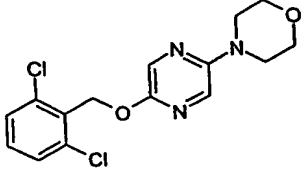
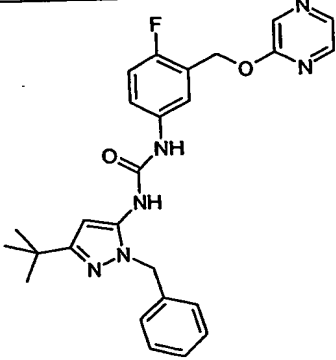
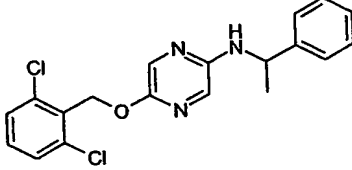
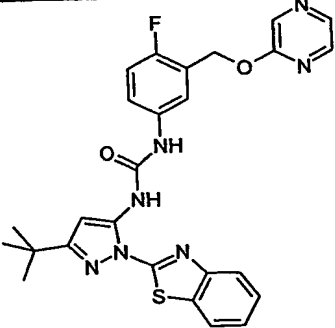
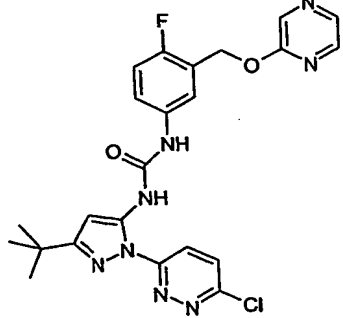
127		<2
128		<2
129		<20
130		<2

131		<20
132		<2
133		<200
134		<2

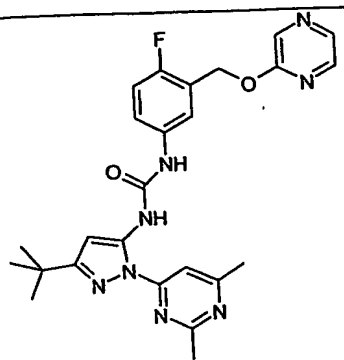
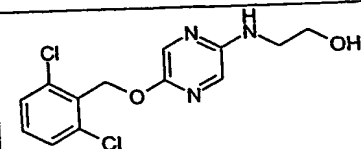
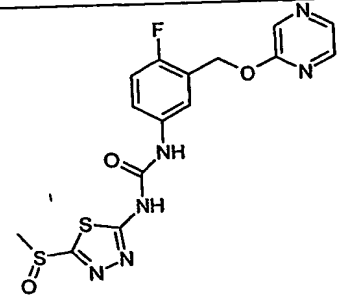
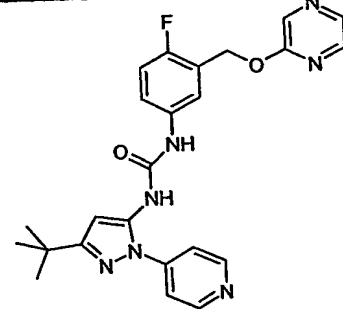
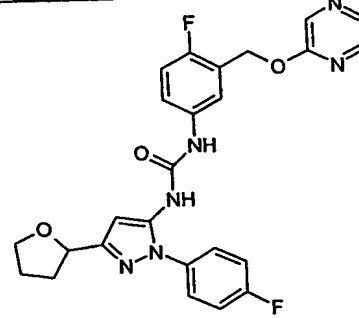
135		<20
136		<20
137		<2
138		<1000
139		<20
140		<2

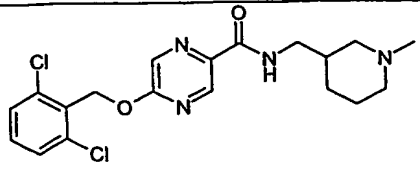
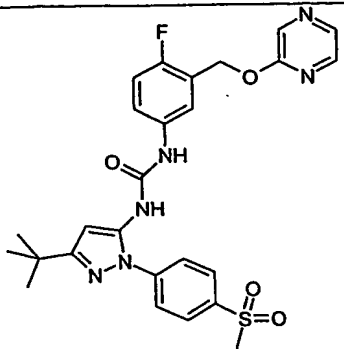
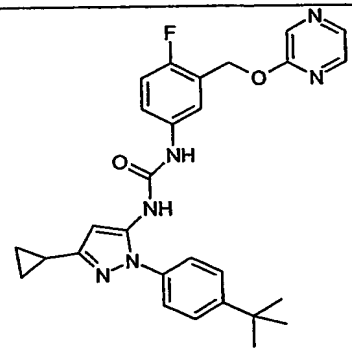
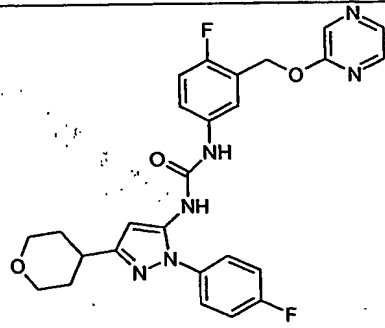
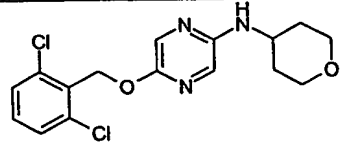
141		<20
142		<200
143		<200
144		<2
145		<200
146		<2

147		<20
148		<200
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150		<2
151		<2

152		<200
153		<2
154		<20
155		<20
156		<2



157		<2
158		<200
159		<1000
160		<2
161		<2

162		<1000
163		<2
164		<200
165		<2
166		<200

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